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⑫

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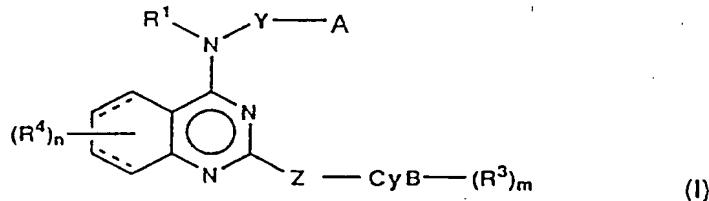
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㉒ 4-Aminoquinazoline derivatives, and their use as medicine.

㉓ The compounds of the formula :



wherein R<sup>1</sup> is H or alkyl ;

Y is bond or alkylene ;

A is

- (i) -CyA-(R<sup>2</sup>)<sub>n</sub>,
- (ii) -O-R<sup>0</sup> or -S(O)p-R<sup>0</sup> or
- (iii) -NR<sup>16</sup>R<sup>17</sup>;

CyA is

(1) 3-7 membered monocyclic carbocyclic ring,

(2) 4-7 membered monocyclic hetero ring containing as hetero atoms, one N atom, one N and one O atoms, two N and one O atoms, or one N and two O atoms,

(3) 4-7 membered monocyclic hetero ring containing as hetero atoms, 1 or 2 O or S atoms ;

R<sup>2</sup> is (1) H, (2) alkyl, (3) alkoxy, (4) -COOR<sup>5</sup>, in which R<sup>5</sup> is H or alkyl, (5) -NR<sup>6</sup>R<sup>7</sup>, (6) -SO<sub>2</sub>NR<sup>8</sup>R<sup>7</sup>, (7) halogen, (8) CF<sub>3</sub>, (9) NO<sub>2</sub> or (10) CF<sub>3</sub>O ;

Z is bond, methylene, ethylene, vinylene or ethynylene ;

R<sup>3</sup> is H, alkyl, alkoxy, halogen or CF<sub>3</sub> ;

and acid addition salts thereof, salts thereof, and hydrates thereof; have inhibitory effect on cGMP-PDE, or additionally on TXA<sub>2</sub> synthetase.

EP 0 579 496 A1

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Serial No.: 09/711,272

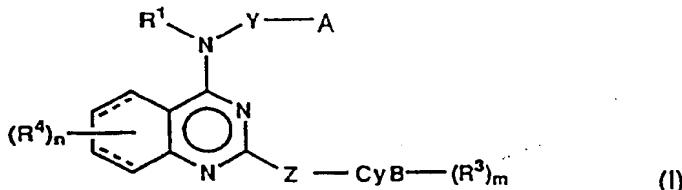
Filed: November 9, 2000

Exhibit 34

The present invention relates to novel 4-aminoquinazoline derivatives. More particularly, this invention relates to:

(i) 4-aminoquinazoline derivatives of the following formula:

5



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wherein all of the symbols have the same meanings as described hereinafter, and the pharmaceutically acceptable acid addition salts thereof, the pharmaceutically acceptable salts thereof, and the hydrates thereof, which have inhibitory activity on cyclic guanosine 3',5'-monophosphate phosphodiesterase, or additionally on thromboxane A<sub>2</sub> synthetase,

20

(ii) processes for the preparation thereof,

25

(iii) inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterase, or additionally of thromboxane A<sub>2</sub> synthetase containing them, and

(iv) methods of prophylactic and curative treatment of mammals, including humans, by administering an effective amount of the compounds of the formula (I), the pharmaceutically acceptable acid addition salts thereof, the pharmaceutically acceptable salts thereof, and the hydrates thereof, to the patient to be treated.

30

Cyclic guanosine 3',5'-monophosphate (abbreviated as cGMP hereafter) was found in urine in rats by D. F. Ashman in 1963. Till now, it has been known that cGMP is distributed broadly in tissues of any animals including human beings. cGMP is biosynthesized from guanosine triphosphate (GTP) by the action of guanylate cyclase.

35

cGMP has been experimentally confirmed to have various physiological activities. For example, cGMP induces the relaxation of heart muscle and of smooth muscle. Further, it is related to the formation of neuronal synapses, and it acts as a trigger of cell proliferation and it induces the proliferation of lymphocyte.

cGMP is metabolized to physiologically inactive 5'-GMP by the action of cGMP phosphodiesterase (abbreviated as cGMP-PDE hereafter).

40

Accordingly, the inhibition of the action of cGMP-PDE is considered to be useful for the prevention and/or treatment of diseases induced by enhancement of the metabolism of cGMP, such as hypertension, heart failure, myocardial infarction, angina, atherosclerosis, cardiac edema, pulmonary hypertension, renal insufficiency, nephrotic edema, hepatic edema, asthma, bronchitis, dementia, immunodeficiency.

45

On the other hand, thromboxane A<sub>2</sub> (abbreviated as TXA<sub>2</sub> hereafter) was found as a constituent of the arachidonate cascade, in platelets by M. Hamberg in 1975. TXA<sub>2</sub> is biosynthesized from arachidonic acid released from cell membrane via prostaglandin G<sub>2</sub> and prostaglandin H<sub>2</sub>, and rapidly metabolized to inactive thromboxane B<sub>2</sub>. TXA<sub>2</sub> is known to induce platelet aggregation and to contract smooth muscle, particularly blood vessel muscle and bronchial muscle. TXA<sub>2</sub> synthetase was isolated and purified from microsome in platelets.

50

Accordingly, the inhibition of TXA<sub>2</sub> synthetase decreases the biosynthesis of TXA<sub>2</sub>, and is useful for the prevention and/or treatment of inflammation, hypertension, thrombosis, arteriosclerosis, cerebral apoplexy, asthma, myocardial infarction, cardiostenosis, cerebral infarction, etc.

55

It is considered that almost any disease occurs by the complex interaction of plural mechanisms. Accordingly, the inhibition of any one of the plural mechanism is not adequate to treat a disease. A medicament inhibiting as many mechanisms as possible, which induce the disease, is considered to be effective and ideal.

Especially, it is very useful for the prevention and/or treatment of diseases induced by platelet aggregation, e.g. angina pectoris, heart failure, pulmonary hypertension and various kinds of renal diseases to have inhibitory active on both cGMP PDE and TXA<sub>2</sub> synthetase.

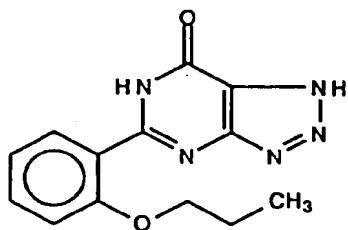
## 55 Related Arts

Up to now, some compounds have been known as cGMP-PDE inhibitors, for example,

## Zaprinast

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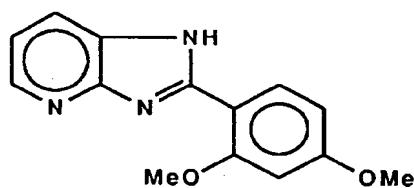
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(A)

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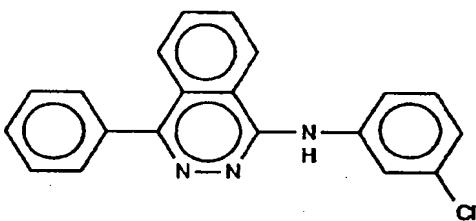
(B)

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## MY-5445

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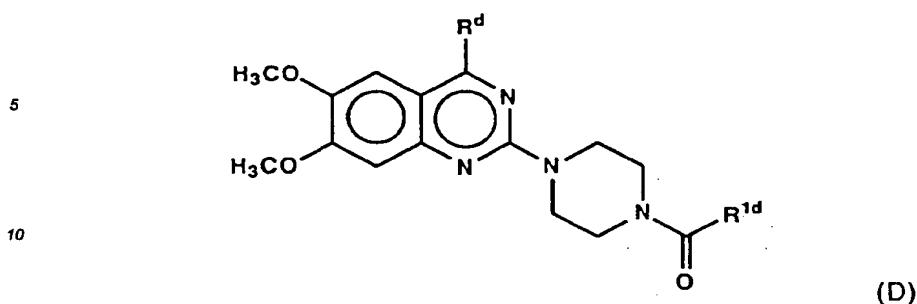


(C)

Many compounds derived from the above lead compounds have been proposed and many patent applications relating to those have been filed. For example, as derivatives of Zaprinast, compounds wherein the 1H-1,2,3-triazole skeleton is replaced by various other hetero cycles (see USP-5047404), those wherein the triazole is replaced by a benzene ring (see EP-371731), and those wherein the triazole is eliminated, i.e. those having only the pyrimidine skeleton (see EP-395328), have been proposed. The above mentioned compounds always contain an oxo group at the 4th position of the pyrimidine skeleton. The compounds having an amino group at the said position are described in USP-4060615. The specification discloses 4-amino-6,7-dimethoxy-2-piperazinylquinazoline derivatives of the following formula:

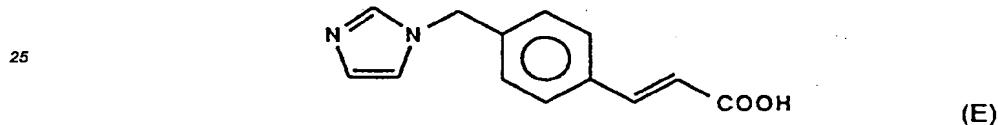
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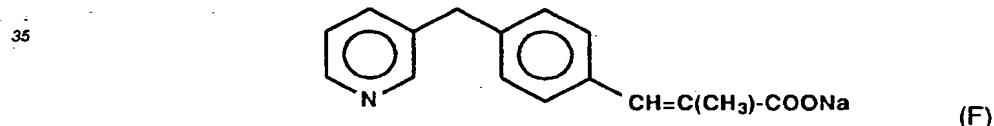


15 wherein Rd is amino or hydrazino,  
R1d is C3-8 cycloalkyl, C3-8 methylcycloalkyl or C4-8 cycloalkenyl,  
and their acid addition salts.  
Furthermore, some TXA<sub>2</sub> synthetase inhibitors have been known, for example,

20 OKY-046



30 ONO-1581

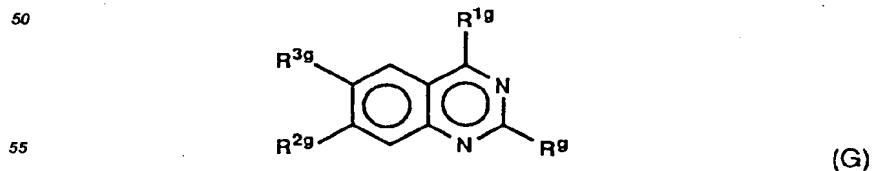


40 Many derivatives containing an imidazole or pyridine ring as the basic skeleton have been proposed. However, there appears to be no TXA<sub>2</sub> synthetase inhibitor having both the said ring and quinazoline ring.

On the other hand, many compounds having a quinazoline ring as the skeleton, which are not known to have inhibitory activity on cGMP-PDE and/or on TXA<sub>2</sub> synthetase, have been proposed.

45 For example, as to 4-aminoquinazoline derivatives having cyclic groups at the 2nd position thereof and as N-substituent,

(1) USP-3772295 discloses the compounds of the formula:



wherein R1g is cyclopentylamino, trifluoromethylanilino, furfurylamino, 3-furylmethylamino, tetrahydrofur-

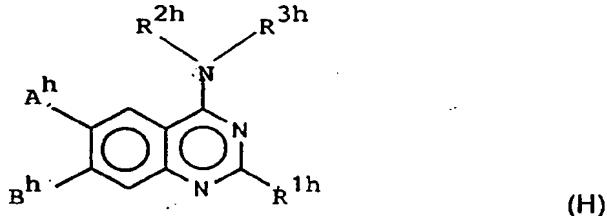
furylamino or tetrahydro-3-furylmethylamino etc;

R<sup>9</sup> is hydrogen, phenyl substituted by one or more methyl, methoxy, chlorine, fluorine or methylenedioxy, a residue derived from furan, thiophene, pyridine, picoline, benzofuran or benzothiophene, or naphthyl;

R<sup>2g</sup> and R<sup>3g</sup> are hydrogen or chlorine;

and their acid addition salts, being useful as diuretics,

(2) GBP-1199768 discloses the compounds of the formula:



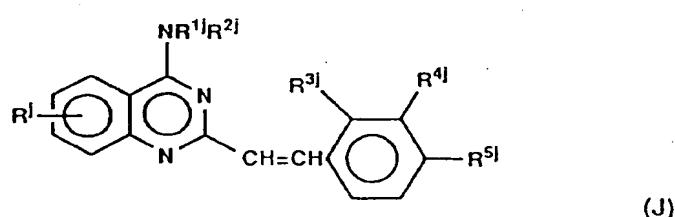
wherein each A<sup>h</sup> and B<sup>h</sup> are C1-5 alkoxy, hydrogen, hydroxy, methyl etc. provided that both A<sup>h</sup> and B<sup>h</sup> are not hydrogen;

20 R<sup>1h</sup> is phenyl, benzyl, phenethyl or substituted phenyl etc.;

each R<sup>2h</sup> and R<sup>3h</sup> are hydrogen, phenyl, phenylalkyl etc.;

and their acid addition salts, being useful as hypotensives or bronchodilators,

(3) Soviet Union Patent No. 461621 discloses the compounds of the formula:



35 wherein R<sup>j</sup> is hydrogen, lower alkyl or lower alkoxy;

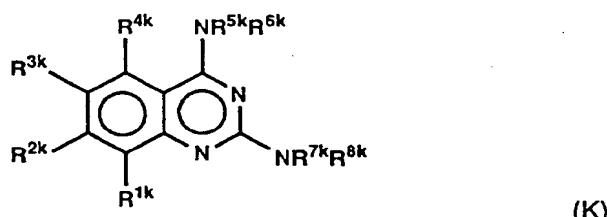
R<sup>1j</sup> is hydrogen or lower alkyl;

R<sup>2j</sup> is phenyl etc.;

R<sup>3j</sup>, R<sup>4j</sup> and R<sup>5j</sup> are hydrogen, halogen, nitro etc.;

and their salts, being useful as a medicine;

40 (4) WO-8905297 discloses the compounds of the formula:



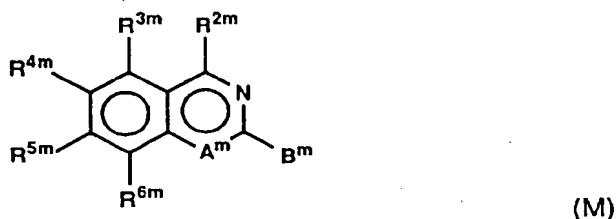
wherein each R<sup>1k</sup>, R<sup>2k</sup>, R<sup>3k</sup> and R<sup>4k</sup> are hydrogen, alkyl, alkoxy, amino, alkylamino, dialkylamino, halogen, trifluoromethyl etc.;

each R<sup>5k</sup> and R<sup>6k</sup> are hydrogen, C1-4 alkyl, -(CH<sub>2</sub>)<sub>n</sub>Ar in which n is 0-4 and Ar is optionally substituted phenyl, etc.;

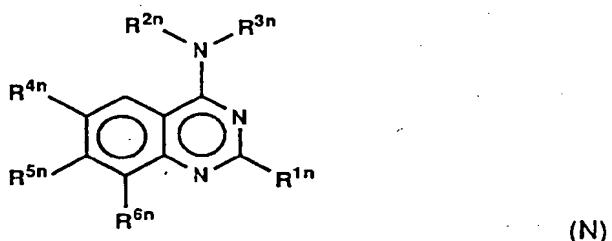
R<sup>7k</sup> and R<sup>8k</sup>, taken together with a nitrogen to which these groups bond, are saturated or unsaturated carbocyclic ring, etc.;

and their salts; having inhibitory effect on H<sup>+</sup>K<sup>+</sup>ATPase and being useful as antiulcer agents.

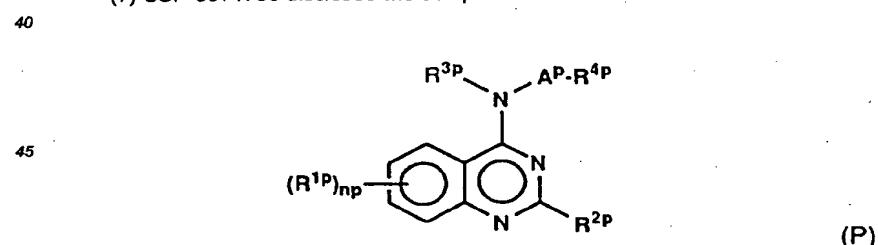
As to 4-aminoquinazoline derivatives having a cyclic group at the 2nd position thereof or as N-substituent,  
 (5) USP-4269834 discloses a complex of a copper salt (III) and the compounds of the formula:



15 wherein A<sup>m</sup> is nitrogen etc.;  
 B<sup>m</sup> is 2-optionally substituted-6-pyridyl or 1,5-optionally substituted-2-imidazolyl;  
 R<sup>2m</sup> is amino, alkylamino, dialkylamino etc.;  
 each R<sup>3m</sup>, R<sup>4m</sup> R<sup>5m</sup> and R<sup>6m</sup> are hydrogen, halogen, alkyl etc.;  
 20 and their acid addition salts, being useful as agents for the treatment of mycoplasma infections,  
 (6) USP-3819628 discloses the compounds of the formula:

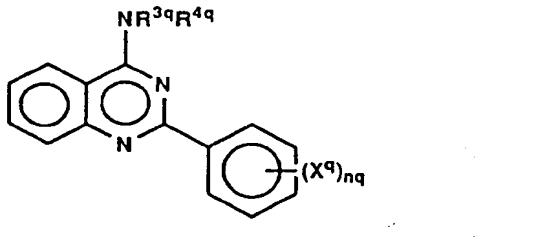


wherein R<sup>1n</sup> is optionally substituted phenyl;  
 35 each R<sup>2n</sup> and R<sup>3n</sup> are hydrogen, C1-4 alkyl, -CH<sub>2</sub>(CH<sub>2</sub>)<sub>n</sub>ONO<sub>2</sub> etc.;  
 each R<sup>4n</sup>, R<sup>5n</sup> and R<sup>6n</sup> are hydrogen, C1-3 alkyl, C1-3 alkoxy etc.;  
 provided that more than two groups are not alkyl;  
 and their salts; being useful as anti-angina agents,  
 (7) USP-3971783 discloses the compounds of the formula:



50 wherein R<sup>1p</sup> is halogen, lower alkyl, lower alkoxy etc.;  
 R<sup>2p</sup> is hydrogen, halogen, lower alkyl, lower alkoxy-lower alkyl etc.;  
 R<sup>3p</sup> is hydrogen, lower alkyl etc.;  
 R<sup>4p</sup> is aromatic N-containing heterocyclic;  
 AP is C1-4 alkylene;  
 55 np is 0-3;  
 and their acid addition salts; being useful as cardiac stimulants,  
 (8) USP-4306055 discloses the compounds of the formula:

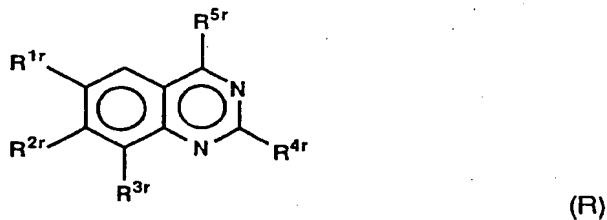
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wherein R<sup>3q</sup> is 4-cyanocycloalkyl-alkyl etc.;  
 R<sup>4q</sup> is hydrogen or alkyl;  
 X<sup>q</sup> is hydrogen, alkyl, alkoxy, nitro, amino or halogen;  
 nq is 1-3;  
 and their acid addition salts and hydrates; being useful as hypotensives,  
 (9) JP Kokai No. 58-172379 discloses the compounds of the formula:

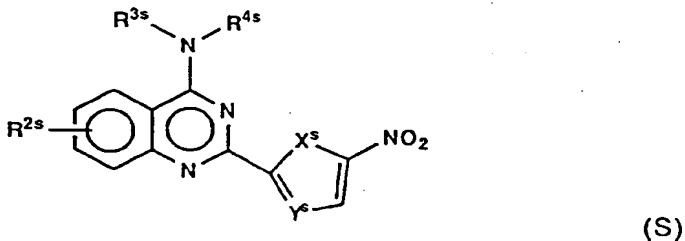
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each R<sup>1r</sup> and R<sup>3r</sup> are lower alkyl;  
 R<sup>2r</sup> is optionally branched alkoxy carbonyl;  
 R<sup>4r</sup> is hydrogen, alkyl or phenyl;  
 R<sup>5r</sup> is amino, alkylamino, dialkylamino etc; being useful as vasodilators,  
 (10) Swiss Patent No. 578556 discloses the compounds of the formula:

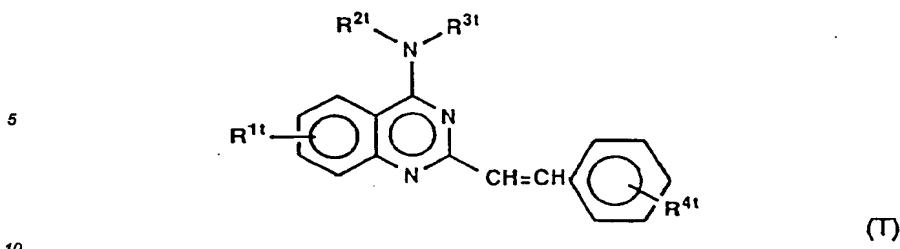
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wherein R<sup>3s</sup> is hydrogen, lower alkyl etc.;  
 R<sup>4s</sup> is hydrogen, amino, lower hydroxylalkyl, lower alkyl etc.;  
 R<sup>2s</sup> is hydrogen, lower alkyl, lower alkoxy etc.;  
 X<sup>s</sup> is -O-, -S- or -N= and Y<sup>s</sup> is -N=, or X<sup>s</sup> is -N= and Y<sup>s</sup> is -CH=;  
 and their acid addition salts; having bactericidal activity,  
 (11) USP-3753981 discloses the compounds of the formula:

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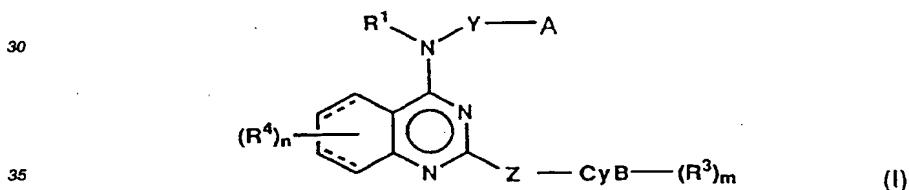


wherein R<sup>1t</sup> is hydrogen, lower alkyl, lower alkoxy etc.;  
each R<sup>2t</sup> and R<sup>3t</sup> are hydrogen, lower alkyl, hydroxy-(lower alkyl) etc.;  
and their acid addition salts; having anti-inflammatory activity.

15 Energetic investigation has been carried out in order to discover compounds having inhibitory activities on cGMP-PDE or additionally TXA<sub>2</sub> synthetase, and as a result, the present inventors have found the compound of the present invention.

20 There is no description of compounds of the formula (I) in any of the related art disclosing compounds in the formulae (D) and (G) to (T) mentioned above. Accordingly, the compounds of the present invention are quite novel. Furthermore, the fact that compounds of the present invention have inhibitory activity on cGMP-PDE or additionally TXA<sub>2</sub> synthetase, is not suggested from pharmaceutical use disclosed in any of the related art mentioned above. Additionally, the inhibitory activity on cGMP-PDE or TXA<sub>2</sub> synthetase, of the compounds of the present invention, is superior to that of the compounds described in any of the related art mentioned above.

25 The present invention relates to:  
(i) quinazoline derivatives of the formula:



wherein R<sup>1</sup> is hydrogen or C<sub>1-4</sub> alkyl;  
Y is single bond or C<sub>1-6</sub> alkylene;  
40 A is  
(i) -CyA-(R<sup>2</sup>)I,  
(ii) -O-R<sup>0</sup> or -S(O)p-R<sup>0</sup>,  
(iii) -NR<sup>16</sup>R<sup>17</sup>;  
in which R<sup>0</sup> is hydrogen, C<sub>1-4</sub> alkyl, hydroxy-C<sub>1-4</sub> alkyl or -CyA-(R<sup>2</sup>)I;  
45 R<sup>16</sup> and R<sup>17</sup> independently are hydrogen or C<sub>1-4</sub> alkyl;  
p is 0-2;  
CyA is  
(1) carbocyclic mono-ring of 3-7 membered, saturated or unsaturated,  
(2) heterocyclic mono-ring of 4-7 membered containing one nitrogen, unsaturated or partially saturated,  
50 (3) heterocyclic mono-ring of 4-7 membered containing one nitrogen and one oxygen, unsaturated or partially saturated,  
(4) heterocyclic mono-ring of 4-7 membered containing one nitrogen and two oxygen, unsaturated or partially saturated,  
(5) heterocyclic mono-ring of 4-7 membered containing two nitrogen and one oxygen, unsaturated or partially saturated,  
55 (6) heterocyclic mono-ring of 4-7 membered containing one or two sulfur, unsaturated or partially saturated or  
(7) heterocyclic mono-ring of 4-7 membered containing one or two oxygen, unsaturated, fully or partially

saturated or saturated;

R<sup>2</sup> is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4) -COOR<sup>5</sup>, in which R<sup>5</sup> is hydrogen or C1-4 alkyl, (5) -NR<sup>6</sup>R<sup>7</sup>, in which R<sup>6</sup> and R<sup>7</sup> independently are hydrogen or C1-4 alkyl, (6) -SO<sub>2</sub>NR<sup>8</sup>R<sup>9</sup>, in which R<sup>8</sup> and R<sup>9</sup> are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro or (10) trifluoromethoxy;

5 Z is single bond, methylene, ethylene (CH<sub>2</sub>CH<sub>2</sub>), vinylene (CH=CH) or ethynylene (C≡C);

CyB is

- (1) heterocyclic mono-ring of 4-7 membered containing one nitrogen, unsaturated or partially saturated,
- (2) heterocyclic mono-ring of 4-7 membered containing two nitrogen, unsaturated or partially saturated,
- (3) heterocyclic mono-ring of 4-7 membered containing three nitrogen, unsaturated or partially saturated,
- (4) heterocyclic mono-ring of 4-7 membered containing one or two oxygen, unsaturated or partially saturated, or
- (5) heterocyclic mono-ring of 4-7 membered containing one or two sulfur, unsaturated or partially saturated;

15 R<sup>3</sup> is hydrogen, C1-4 alkyl, C1-4 alkoxy, halogen or trifluoromethyl;

R<sup>4</sup> is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4) -COOR<sup>8</sup>, in which R<sup>8</sup> is hydrogen or C1-4 alkyl, (5) -NR<sup>9</sup>R<sup>10</sup>, in which R<sup>9</sup> is hydrogen, C1-4 alkyl or phenyl(C1-4 alkyl) and R<sup>10</sup> is hydrogen or C1-4 alkyl, (6) -NHCOR<sup>11</sup>, in which R<sup>11</sup> is C1-4 alkyl, (7) -NHSO<sub>2</sub>R<sup>11</sup>, in which R<sup>11</sup> is as hereinbefore defined, (8) SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, in which R<sup>9</sup> and R<sup>10</sup> are as hereinbefore defined, (9) -OCOR<sup>11</sup>, in which R<sup>11</sup> is as hereinbefore defined, (10) halogen, (11) trifluoromethyl, (12) hydroxy, (13) nitro, (14) cyano, (15) -SO<sub>2</sub>N=CHNR<sup>12</sup>R<sup>13</sup> in which R<sup>12</sup> is hydrogen or C1-4 alkyl and R<sup>13</sup> is C1-4 alkyl, (16) -CONR<sup>14</sup>R<sup>15</sup> in which R<sup>14</sup> is hydrogen or C1-4 alkyl or phenyl(C1-4 alkyl) and R<sup>15</sup> is C1-4 alkyl or (17) C1-4 alkylthio, (18) C1-4 alkylsulfinyl, (19) C1-4 alkylsulfonyl, (20) ethynyl, (21) hydroxymethyl, (22) tri(C1-4 alkyl)silylethynyl or (23) acetyl;

20 and I, m and n independently are 1 or 2;

25 with the proviso that

- (1) the group of the formula: -CyA-(R<sup>2</sup>), does not represent a cyclopentyl or trifluoromethylphenyl group when Y is a single bond, that

20 (2) a CyB ring should not bond to Z through a nitrogen atom in the CyB ring when Z is vinylene or ethynylene, that

30 (3) a CyB ring should not represent pyridine or thiophene when CyA is a ring of CyA-(7) and that

(4) Y is not a single bond, when A is (ii) -O-R<sup>0</sup> or -S(O)p-R<sup>0</sup> or (iii) -NR<sup>16</sup>R<sup>17</sup>; and pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, and hydrates thereof,

(ii) process for the preparation thereof,

35 (iii) cGMP-PDE inhibitors, or additionally TXA<sub>2</sub> synthetase inhibitors, containing them as active ingredient, and

(iv) methods of prophylactic and curative treatment of mammals, including humans, by administering an effective amount of the compounds of the formula (I), the pharmaceutically acceptable acid addition salts thereof, the pharmaceutically acceptable salts thereof, and the hydrates thereof, to the patient to be treated.

40 In the formula (I), the C1-4 alkyl group represented by R<sup>0</sup>, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> mean methyl, ethyl, propyl, butyl and the isomers thereof.

In the formula (I), the C1-4 alkoxy group represented by R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> mean methoxy, ethoxy, propoxy, butoxy and isomers thereof.

45 In the formula (I), the halogen atom represented by R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> mean fluorine, chlorine, bromine and iodine.

In the formula (I), the C1-6 alkylene group represented by Y means methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene and isomers thereof.

50 In the formula (I), examples of 3-7 membered, saturated or unsaturated, monocyclic carbocyclic ring, represented by CyA-(1), are cyclobutadiene, cyclopentadiene, benzene, cycloheptatriene ring, and partially or fully saturated rings thereof, for example, cyclobutane, cyclopentane, cyclohexane, cycloheptane ring, and cyclopropane ring.

In the formula (I), heterocyclic mono-ring of 4-7 membered containing one nitrogen atom, unsaturated or partially saturated represented by CyA-(2) and CyB-(1) is, for example, azepine, pyridine, pyrrole, isomeric rings thereof and partially saturated rings thereof.

55 In the formula (I), heterocyclic mono-ring of 4-7 membered containing one nitrogen atom and one oxygen atom, unsaturated or partially saturated represented by CyA-(3) is, for example, oxyazepine, oxazine, oxyazole, isomeric rings thereof and partially saturated rings thereof.

In the formula (I), heterocyclic mono-ring of 4-7 membered containing one nitrogen atom and two oxygen atom, unsaturated or partially saturated represented by CyA-(4) is, for example, dioxazepine, dioxazine, diazole, isomeric rings thereof and partially saturated rings thereof.

In the formula (I), heterocyclic mono-ring of 4-7 membered containing two nitrogen atom and one oxygen atom, unsaturated or partially saturated represented by CyA-(5) is, for example, oxadiazepine, oxadiazine, oxadiazole, isomeric rings thereof and partially saturated rings thereof.

In the formula (I), heterocyclic mono-ring of 4-7 membered containing one or two sulfur atom, unsaturated or partially saturated represented by CyA-(6) and CyB-(5) is, for example, thiepin, thiophene, thiain, dithian, isomeric rings thereof and partially saturated rings thereof.

In the formula (I), heterocyclic mono-ring of 4-7 membered containing two oxygen atoms, unsaturated or fully or partially saturated represented by CyA-(7) is, for example, oxepin, pyran, dioxin, furan, isomeric rings thereof and fully or partially saturated rings thereof.

In the formula (I), heterocyclic mono-ring of 4-7 membered containing one or two oxygen atoms, unsaturated or partially saturated represented by CyB-(4) is, for example, oxepin, pyran, dioxin, furan, isomeric rings thereof or partially saturated rings thereof.

In the formula (I), heterocyclic mono-ring of 4-7 membered containing two nitrogen atoms, unsaturated or partially saturated represented by CyB-(2) is, for example, diazepine, diazine, diazole, isomeric rings thereof or partially saturated rings thereof.

In the formula (I), heterocyclic mono-ring of 4-7 membered containing three nitrogen atoms, unsaturated or partially saturated represented by CyB-(3) is, for example, triazepine, triazine, triazole, isomeric rings thereof and partially saturated rings thereof.

Examples of representative compounds of the present invention are listed as follows:

- 1 4-phenylmethylamino-2-(3-pyridyl)quinazoline,
- 2 4-(3-methylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
- 3 4-(3,4-dimethoxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,
- 4 4-(4-carboxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,
- 5 4-(3-methoxycarbonylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
- 6 4-(4-(N,N-dimethylamino)phenylmethyl)amino-2-(3-pyridyl)-quinazoline,
- 7 4-(4-sulfamoylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
- 8 4-(3-chlorophenylmethyl)amino-2-(3-pyridyl)quinazoline,
- 9 4-(3-trifluoromethylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
- 10 4-(3-nitrophenylmethyl)amino-2-(3-pyridyl)quinazoline,
- 11 4-phenylmethylamino-2-(6-methyl-3-pyridyl)quinazoline,
- 12 4-phenylmethylamino-2-(6-methoxy-3-pyridyl)quinazoline,
- 13 4-phenylmethylamino-2-(6-chloro-3-pyridyl)quinazoline,
- 14 4-phenylmethylamino-2-(6-trifluoromethyl-3-pyridyl)quinazoline,
- 15 4-phenylmethylamino-6-methyl-2-(3-pyridyl)quinazoline,
- 16 4-phenylmethylamino-6-methoxy-2-(3-pyridyl)quinazoline,
- 17 4-phenylmethylamino-6,7-dimethoxy-2-(3-pyridyl)quinazoline,
- 18 4-phenylmethylamino-6-carboxy-2-(3-pyridyl)quinazoline,
- 19 4-phenylmethylamino-6-methoxycarbonyl-2-(3-pyridyl)quinazoline,
- 20 4-phenylmethylamino-6-amino-2-(3-pyridyl)quinazoline,
- 21 4-phenylmethylamino-6-(N,N-dimethylamino)-2-(3-pyridyl)quinazoline,
- 22 4-phenylmethylamino-6-acetylamino-2-(3-pyridyl)quinazoline,
- 23 4-phenylmethylamino-6-methanesulfonylamino-2-(3-pyridyl)quinazoline,
- 24 4-phenylmethylamino-6-sulfamoyl-2-(3-pyridyl)quinazoline,
- 25 4-phenylmethylamino-6-acetoxy-2-(3-pyridyl)quinazoline,
- 26 4-phenylmethylamino-6-chloro-2-(3-pyridyl)quinazoline,
- 27 4-phenylmethylamino-6-bromo-2-(3-pyridyl)quinazoline,
- 28 4-phenylmethylamino-7-fluoro-2-(3-pyridyl)quinazoline,
- 29 4-phenylmethylamino-6-trifluoromethyl-2-(3-pyridyl)quinazoline,
- 30 4-phenylmethylamino-6-hydroxy-2-(3-pyridyl)quinazoline,
- 31 4-phenylmethylamino-6-nitro-2-(3-pyridyl)quinazoline,
- 32 4-phenylmethylamino-6-cyano-2-(3-pyridyl)quinazoline,
- 33 4-phenylmethylamino-6-methyl-2-(4-pyridyl)quinazoline,
- 34 4-phenylmethylamino-6-methoxy-2-(4-pyridyl)quinazoline,
- 35 4-phenylmethylamino-6,7-dimethoxy-2-(4-pyridyl)quinazoline,
- 36 4-phenylmethylamino-6-carboxy-2-(4-pyridyl)quinazoline,

37 4-phenylmethylamino-6-methoxycarbonyl-2-(4-pyridyl)quinazoline,  
 38 4-phenylmethylamino-6-amino-2-(4-pyridyl)quinazoline,  
 39 4-phenylmethylamino-6-(N,N-dimethylamino)-2-(4-pyridyl)quinazoline,  
 40 4-phenylmethylamino-6-acetylamino-2-(4-pyridyl)quinazoline,  
 5 41 4-phenylmethylamino-6-methanesulfonylamino-2-(4-pyridyl)quinazoline,  
 42 4-phenylmethylamino-6-sulfamoyl-2-(4-pyridyl)quinazoline,  
 43 4-phenylmethylamino-6-acetoxy-2-(4-pyridyl)quinazoline,  
 44 4-phenylmethylamino-6-chloro-2-(4-pyridyl)quinazoline,  
 45 4-phenylmethylamino-6-bromo-2-(4-pyridyl)quinazoline,  
 10 46 4-phenylmethylamino-7-fluoro-2-(4-pyridyl)quinazoline,  
 47 4-phenylmethylamino-6-trifluoromethyl-2-(4-pyridyl)quinazoline,  
 48 4-phenylmethylamino-6-hydroxy-2-(4-pyridyl)quinazoline,  
 49 4-phenylmethylamino-6-nitro-2-(4-pyridyl)quinazoline,  
 50 4-phenylmethylamino-6-cyano-2-(4-pyridyl)quinazoline,  
 15 51 4-phenylmethylamino-6-methyl-2-(1-imidazolyl)quinazoline,  
 52 4-phenylmethylamino-6-methoxy-2-(1-imidazolyl)quinazoline,  
 53 4-phenylmethylamino-6,7-dimethoxy-2-(1-imidazolyl)quinazoline  
 54 4-phenylmethylamino-6-carboxy-2-(1-imidazolyl)quinazoline,  
 55 4-phenylmethylamino-6-methoxycarbonyl-2-(1-imidazolyl)quinazoline,  
 20 56 4-phenylmethylamino-6-amino-2-(1-imidazolyl)quinazoline,  
 57 4-phenylmethylamino-6-(N',N'-dimethylamino)-2-(1-imidazolyl)quinazoline,  
 58 4-phenylmethylamino-6-acetylamino-2-(1-imidazolyl)quinazoline,  
 59 4-phenylmethylamino-6-methanesulfonylamino-2-(1-imidazolyl)quinazoline,  
 60 4-phenylmethylamino-6-sulfamoyl-2-(1-imidazolyl)quinazoline,  
 25 61 4-phenylmethylamino-6-acetoxy-2-(1-imidazolyl)quinazoline,  
 62 4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline,  
 63 4-phenylmethylamino-6-bromo-2-(1-imidazolyl)quinazoline,  
 64 4-phenylmethylamino-7-fluoro-2-(1-imidazolyl)quinazoline,  
 65 4-phenylmethylamino-6-trifluoromethyl-2-(1-imidazolyl)quinazoline,  
 30 66 4-phenylmethylamino-6-hydroxy-2-(1-imidazolyl)quinazoline,  
 67 4-phenylmethylamino-6-nitro-2-(1-imidazolyl)quinazoline,  
 68 4-phenylmethylamino-6-cyano-2-(1-imidazolyl)quinazoline,  
 69 4-phenylamino-2-(3-pyridyl)quinazoline,  
 70 4-(3-methoxycarbonylphenyl)amino-2-(3-pyridyl)quinazoline,  
 35 71 4-phenethylamino-2-(3-pyridyl)quinazoline,  
 72 4-(cyclopropylmethyl)amino-2-(3-pyridyl)quinazoline,  
 73 4-(cyclohexylmethyl)amino-2-(3-pyridyl)quinazoline,  
 74 4-(2-azepinylmethyl)amino-2-(3-pyridyl)quinazoline,  
 75 4-(3-pyridylmethyl)amino-2-(3-pyridyl)quinazoline,  
 40 76 4-((1-methyl-2-pyrrolyl)methyl)amino-2-(3-pyridyl)quinazoline,  
 77 4-(3-isoxazolylmethyl)amino-2-(3-pyridyl)quinazoline,  
 78 4-(3-isoxazolylmethyl)amino-2-(3-pyridyl)quinazoline,  
 79 4-(2-thienylmethyl)amino-2-(3-pyridyl)quinazoline,  
 80 4-phenylmethylamino-2-(2-azepinyl)quinazoline,  
 45 81 4-phenylmethylamino-2-(1,5-diazepin-2-yl)quinazoline,  
 82 4-phenylmethylamino-2-(2-pyrimidinyl)quinazoline,  
 83 4-phenylmethylamino-2-(2-triazinyl)quinazoline,  
 84 4-phenylmethylamino-2-(2-pyridyl)quinazoline,  
 85 4-phenylmethylamino-2-(4-pyridyl)quinazoline,  
 50 86 4-phenylmethylamino-2-(2-(3-pyridyl)ethyl)quinazoline,  
 87 4-phenylmethylamino-2-(2-(3-pyridyl)vinyl)quinazoline,  
 88 4-phenylmethylamino-2-(2-pyrrolyl)quinazoline,  
 89 4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 90 4-phenylmethylamino-2-((1-imidazolyl)methyl)quinazoline,  
 55 91 4-phenylmethylamino-2-(2-methyl-1-imidazolyl)quinazoline,  
 92 4-phenylmethylamino-2-(1-triazolyl)quinazoline,  
 93 4-phenylmethylamino-2-(2-thienyl)quinazoline,  
 94 4-phenylmethylamino-2-(2-furyl)quinazoline,

95 6-methyl-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-quinazoline  
 96 6,7-dimethoxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-quinazoline  
 97 6-acetoxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-quinazoline,  
 98 6-chloro-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-quinazoline,  
 99 6-bromo-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-quinazoline,  
 100 6-iodo-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-quinazoline,  
 101 7-fluoro-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-quinazoline,  
 102 6-hydroxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-quinazoline,  
 103 6-nitro-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-quinazoline,  
 104 6-methyl-4-(2-methoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 105 6,7-dimethoxy-4-(2-methoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 106 6-acetoxy-4-(2-methoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 107 6-chloro-4-(2-methoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 108 6-bromo-4-(2-methoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 109 6-iodo-4-(2-methoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 110 7-fluoro-4-(2-methoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 111 6-hydroxy-4-(2-methoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 112 6-nitro-4-(2-methoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 113 6-chloro-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)-quinazoline,  
 114 6-methyl-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)-quinazoline,  
 115 6-methoxy-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)-quinazoline,  
 116 6,7-dimethoxy-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)-quinazoline,  
 117 6-acetoxy-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)-quinazoline,  
 118 6-chloro-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)-quinazoline,  
 119 6-bromo-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)-quinazoline,  
 120 6-iodo-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)-quinazoline,  
 121 7-fluoro-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)-quinazoline,  
 122 6-hydroxy-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)-quinazoline,  
 123 6-nitro-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)-quinazoline,  
 124 6-methyl-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 125 6-methoxy-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 126 6,7-dimethoxy-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 127 6-acetoxy-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 128 6-chloro-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 129 6-bromo-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 130 6-iodo-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 131 7-fluoro-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 132 6-hydroxy-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 133 6-nitro-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)-quinazoline,  
 134 6-methyl-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-quinazoline,  
 135 6-methoxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-quinazoline,  
 136 6,7-dimethoxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-quinazoline,  
 137 6-acetoxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-quinazoline,  
 138 6-bromo-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-quinazoline,  
 139 6-iodo-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-quinazoline,  
 140 7-fluoro-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-quinazoline,  
 141 6-hydroxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-quinazoline,  
 142 6-nitro-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-quinazoline,

and further those described in Examples below are also representative compounds of the present invention.

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#### Salts and Acid addition salts

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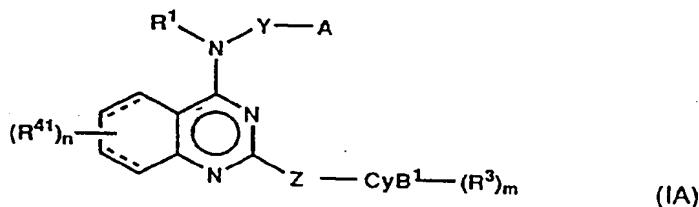
The compounds of the formula (I), if desired, may be converted into acid addition salts by known methods. Preferably, acid addition salts are non-toxic and water-soluble. The suitable acid addition salts are, for example, salts of an inorganic acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, nitric acid, or an organic acid such as acetic acid, lactic acid, tartaric acid, benzoic acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, isethionic acid, glucuronic acid and gluconic acid.

The compounds of the formula (I), if desired, may be converted into salts by known methods. Preferable, salts are non-toxic salts and water-soluble. The suitable salts are salts of alkaline metal (sodium, potassium etc.), salts of alkaline earth metal (calcium, magnesium etc.), ammonium salts, salts of pharmaceutically acceptable organic amine (tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, phenylmethylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)methylamine, lysine, arginine, N-methyl-D-glucamine etc.).

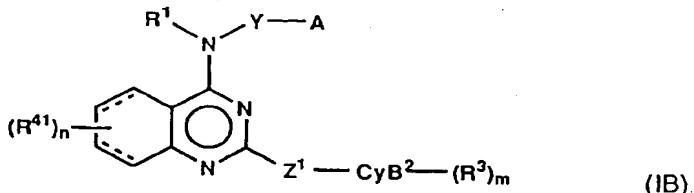
Throughout the specification including claims, it may be easily understood by those skilled in the art, that the alkyl, alkoxy, groups include straight- chained and also branched-chained ones. Accordingly, all isomers produced by the difference in stereo configuration, such as asymmetric carbons are included in the present invention.

### Preparations

According to the present invention, of the compounds of the present invention, the compounds of the formula:



wherein R⁴¹ is (1) hydrogen, (2) C<sub>1-4</sub> alkyl, (3) C<sub>1-4</sub> alkoxy, (4) -COOR⁸, (5) -NR⁹R¹⁰, in which R⁹ and R¹⁰ are as hereinbefore defined, provided that both R⁹ and R¹⁰ are not hydrogen, (6) SO<sub>2</sub>NR⁹R¹⁰, in which R⁹ and R¹⁰ are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro, (10) cyano, (11) C<sub>1-4</sub> alkylthio, (12) tri(C<sub>1-4</sub> alkyl)silylethynyl, (13) -SO<sub>2</sub>N = CHNR¹²R¹³, in which R¹² and R¹³ are as hereinbefore defined, or (14) -CONR¹⁴R¹⁵, in which R¹⁴ and R¹⁵ are as hereinbefore defined, CyB¹ is as hereinbefore defined for CyB, provided that a carbon atom in the ring should bond to Z, and the other symbols are as hereinbefore defined; and the compounds of the formula:



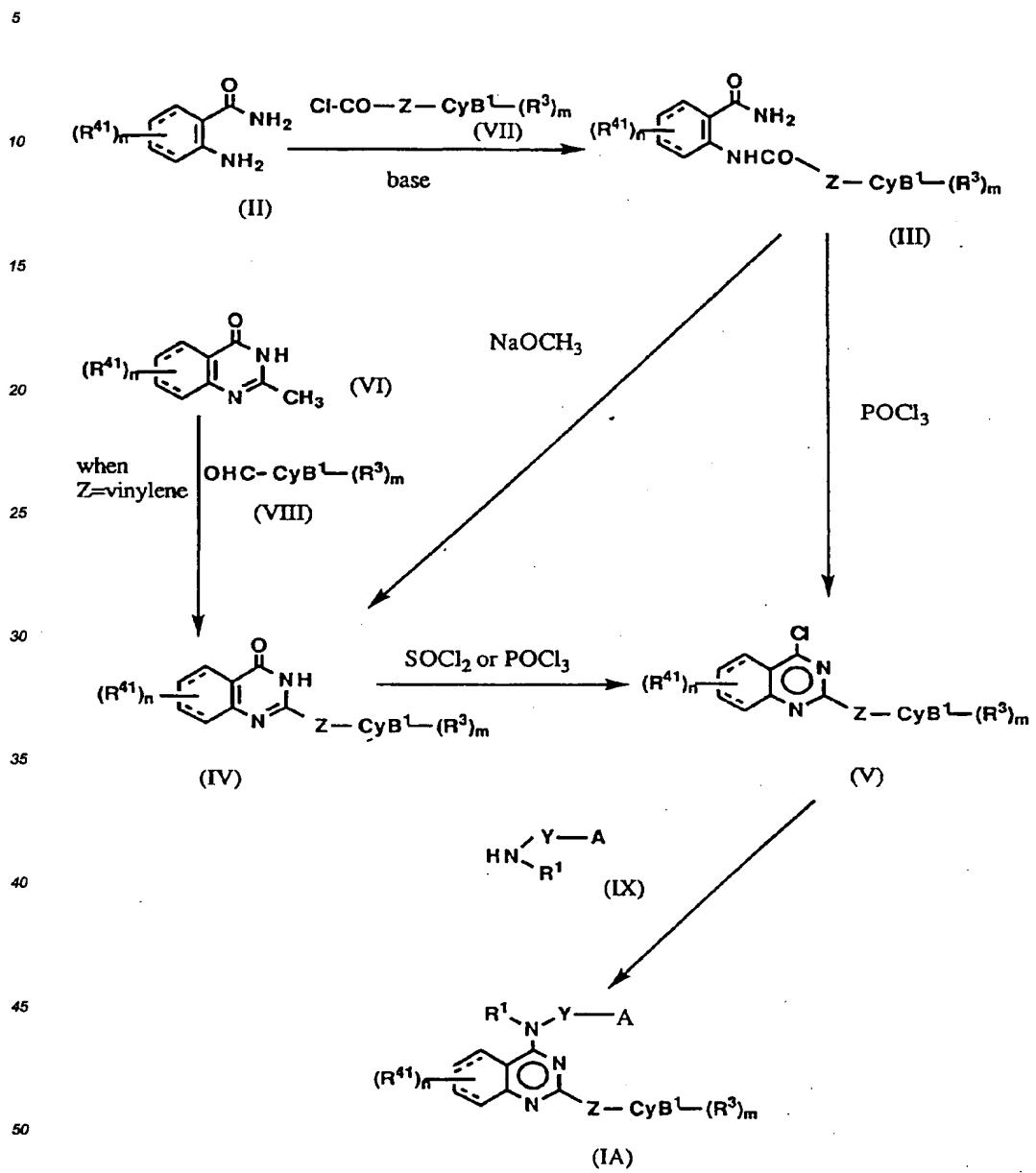
45 wherein Z¹ is single bond or methylene, CyB² is as hereinbefore defined for CyB, provided that a nitrogen atom in the ring should bond to Z¹,

and the other symbols are as hereinbefore defined; may be prepared by using a series of reactions depicted in Scheme A and B, respectively, wherein R⁵⁰ is C<sub>1-4</sub> alkyl and the other symbols are as hereinbefore defined.

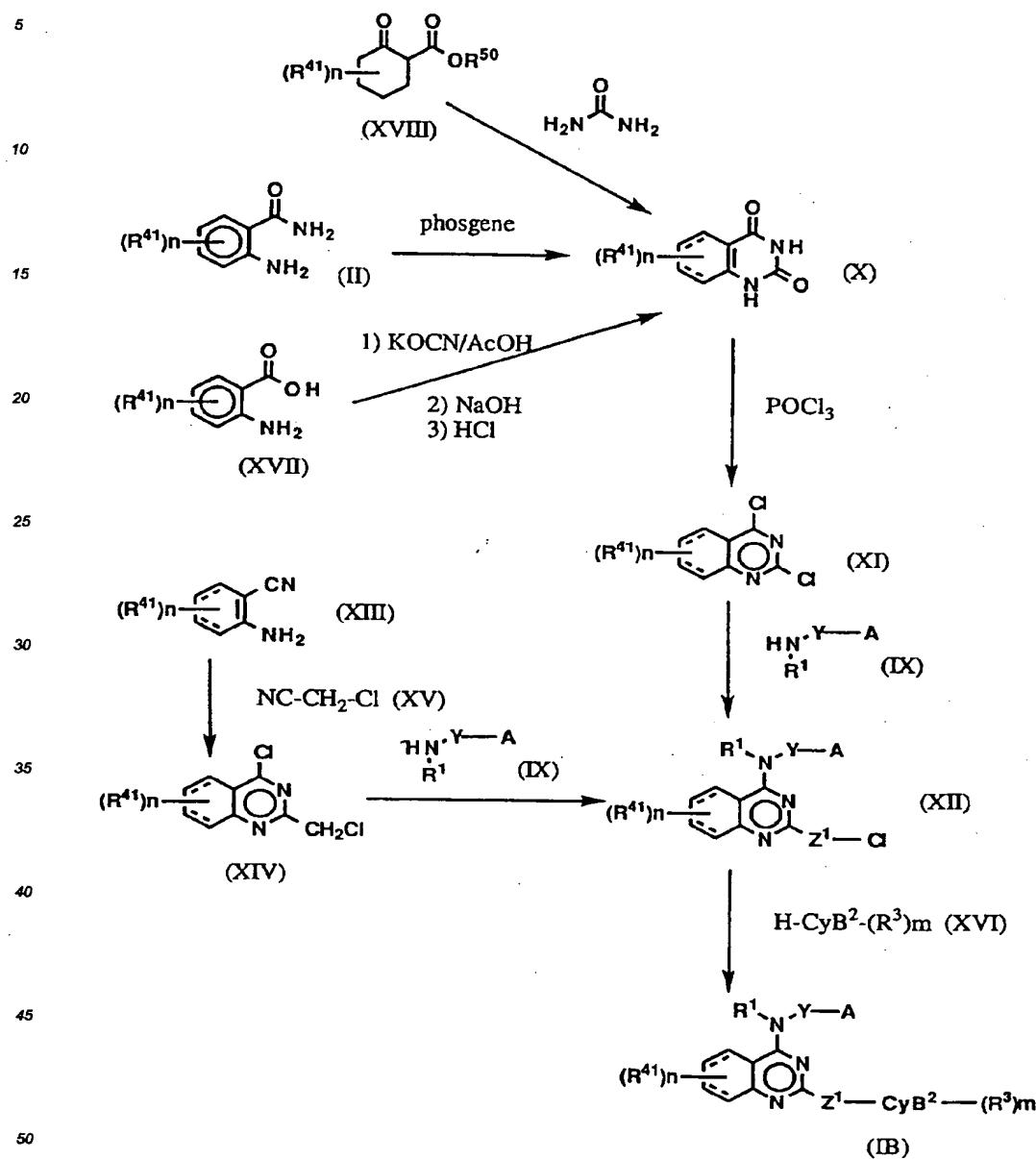
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Scheme A



Scheme B



Each reaction in Scheme A and B may be carried out by methods known per se, under conditions described therein.

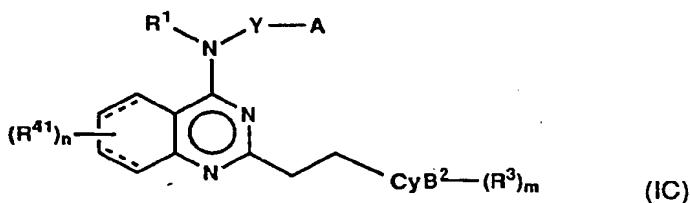
For example, the compounds of the formula (IA) may be prepared from those of the formula (V) by the reaction with an amine of the formula (IX) in a proper organic solvent such as a lower alkanol (e.g. ethanol) or tetrahydrofuran, or a mixture thereof, at a temperature from ambient to reflux, for several hours to several

days, if necessary in the presence of a base such as triethylamine.

Further, the compounds of the formula (IB) may be prepared from those of the formula (XII) by the reaction with a cyclic amine of the formula (XVI) in phenol at a reflux temperature for several hours.

Furthermore, the compounds of the present invention, of the formula:

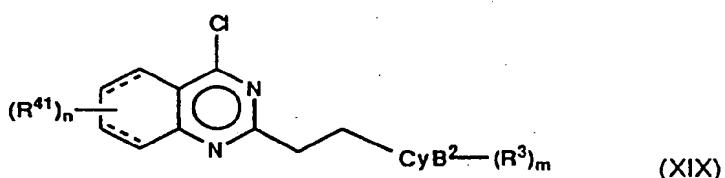
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wherein the various symbols are as hereinbefore defined; may be prepared from those of the formula:

20



wherein the various symbols are as hereinbefore defined; by the methods described hereinbefore for the conversion of the compounds of the formula (V) into those of the formula (IA). The compounds of the formula (XIX) may be prepared by the methods similar to those described hereinbefore in Scheme A.

30

On the other hand, the compounds of the formula (I) other than those of the formulae (IA), (IB) and (IC) may be prepared by the methods known per se described below.

The compounds of the formula (I) wherein R⁴ is amino may be prepared from those wherein R⁴ is nitro, by the reduction with zinc etc. in a proper organic solvent.

35

The compounds of the formula (I) wherein R⁴ is hydroxy may be prepared from those wherein R⁴ is alkoxy such as methoxy, by the reaction with hydrogen bromide or tribromoborron.

The compounds of the formula (I) wherein R⁴ is -NHCOR¹¹, wherein R¹¹ is as hereinbefore defined, may be prepared from those wherein R⁴ is nitro, by the reaction with the corresponding organic acid such as acetic acid in the presence of zinc dust.

40

The compounds of the formula (I) wherein R⁴ is NHSO₂R¹¹, wherein R¹¹ is as hereinbefore defined, may be prepared from those wherein R⁴ is amino by the reaction with the corresponding alkylsulfonyl chloride such as methanesulfonyl chloride.

The compounds of the formula (I) wherein R⁴ is -OCOR¹¹, wherein R¹¹ is as hereinbefore defined, may be prepared from those wherein R⁴ is hydroxy by the esterification with the corresponding organic acid such as acetic acid.

45

The compounds of the formula (I) wherein R⁴ is C1-4 alkylsulfinyl or C1-4 alkylsulfonyl may be prepared from those wherein R⁴ is C1-4 alkylthio by the oxidation by oxidizing agent such as hydrogen peroxide.

The compounds of the formula (I) wherein R⁴ is hydroxymethyl may be prepared from those wherein R⁴ is alkoxy carbonyl, by the reduction with reducing agent such as lithium borohydride, lithium aluminum hydride etc.

50

The compounds of the formula (I) wherein R⁴ is ethynyl may be prepared from those wherein R⁴ is tri(C1-4 alkyl)silylethynyl, by the removal reaction of silyl group with tetrabutylammonium halide.

The compounds of the formula (I) wherein R⁴ is acetyl may be prepared from those wherein R⁴ is ethynyl, by the reaction with mercury sulfate and acetic acid in an acidic condition.

55

In each reaction in the present specification, products may be purified by conventional manner. For example, it may be carried out by distillation at atmospheric or reduced pressure, high performance liquid chromatography, thin layer chromatography or column chromatography using silica gel or magnesium silicate, washing or recrystallization. Purification may be carried out after each reaction, or after a series of reactions. The starting materials of the formulae (II), (VI) and (XIII), and each reagents of the formulae (VII), (VIII),

(IX), (XV), (XVI), (XVII) and (XVIII) used in the process for the preparation of the present invention are known per se or may be easily prepared by known methods.

#### Effect

The compounds of the formula (I), pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, or hydrates thereof, of the present invention have an inhibitory effect on cGMP-PDE, or additionally on TXA<sub>2</sub> synthetase, and are, therefore, useful for the prevention and/or treatment of not only diseases induced by enhancement of the metabolism of cGMP, such as hypertension, heart failure, myocardial infarction, angina, atherosclerosis, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, asthma, bronchitis, dementia, immunodeficiency, but also diseases induced by enhancement of the synthesis of TXA<sub>2</sub> such as inflammation, thrombosis, cerebral apoplexy, asthma, cardiostenosis, cerebral infarction etc, in mammals, especially in humans.

Especially, it is very useful for the prevention and/or treatment of heart failure, angina pectoris, pulmonary hypertension, various kinds of renal diseases, hyoioresis induced by heart failure.

The inhibitory effect on cGMP-PDE and TXA<sub>2</sub> synthetase, of the compounds of the present invention were confirmed by screening tests as described below.

#### (1) Inhibitory effect on cGMP-PDE

##### Method

PDE IC was isolated from human platelets according to standard methods previously described in Lugnier, C. et al., *Biochem. Pharmacol.* 35: 1743, 1986 (incorporated in its entirety by reference). Typically, connective tissue and adventitia were removed and 1-2 units of platelets were suspended in 10 volumes of buffer A (20 mM Tris-HCl, pH 7.5, containing 2 mM magnesium acetate, 1 mM dithiothreitol, and 5 mM Na2EDTA) using a Brinkman polytron. The proteinase inhibitors leupeptin, pepstatin A, and phenylmethyl-sulfonyl fluoride (PMSF) were also included in this buffer (final concentration of 100 nM each). The homogenate was centrifuged at 100,000g for 60 minutes. The supernatant was then removed and filtered through four layers of cheesecloth.

The supernatant was applied to a DWAE-Trisacryl M column. The column was washed with several bed volumes of buffer B (20 mM Tris-HCl, pH 7.5, containing 2 mM magnesium acetate, 1 mM dithiothreitol, and proteinase inhibitors) and eluted by two successive linear NaCl gradients (0.05-0.15 M, 300 ml total; 0.15-0.40 M, 200 ml total). Five milliliterfractions were collected and assayed for cyclic GMP PDE activity.

Phosphodiesterase activity was measured, as described by Thompson, et al., *Adv. Cyclic Nucleotide Res.* 10: 69, 1979 (incorporated in its entirety by reference), in a reaction medium containing 40 mM Tris-HCl (pH 8.0), 5 mM MgCl<sub>2</sub>, and 1 mM dithiothreitol. The concentration of substrate (<sup>3</sup>H-cGMP) was 0.2mM. Compounds of the present invention were dissolved in dimethyl sulfoxide (DMSO) at a final concentration of 2.5%. This concentration of DMSO inhibited enzyme activity by approximately 10%. The IC<sub>50</sub> values (concentration that produced 50% inhibition of substrate hydrolysis) for the compounds examined were determined from concentration-response curves in which concentrations typically ranged from 10<sup>-8</sup> to 10<sup>-3</sup> M for the less potent inhibitors (half-log increments).

##### Result

The result is shown in Table 1 below.

Table 1 : Inhibitory activity on cGMP-PDE

	Compounds Example No.	Inhibitory activity IC <sub>50</sub> , (M)
5	3 (e) (free base)	4.5 x 10 <sup>-7</sup>
	3 (i) (2HCl)	3.6 x 10 <sup>-7</sup>
	3 (ee) (2HCl)	3.0 x 10 <sup>-7</sup>
10	3 (k) (3HCl)	2.8 x 10 <sup>-6</sup>
	7 (free base)	2.0x 10 <sup>-7</sup>
	5 (free base)	2.6x 10 <sup>-7</sup>
15	3 (t) (free base)	7.2x 10 <sup>-7</sup>
	3(l) (2HCl)	7.6x 10 <sup>-7</sup>
	6 (b) (2HCl)	3.0x 10 <sup>-6</sup>
20	6 (a) (2HCl)	2.8x 10 <sup>-9</sup>
	3 (a) (2HCl)	1.05x 10 <sup>-7</sup>
	3 (z) (2HCl)	1.0x 10 <sup>-6</sup>
25	3(ff) (2HCl)	4.2x10 <sup>-9</sup>
	6(c) (2HCl)	2.3x10 <sup>-9</sup>
	6(k) (2HCl)	6.3x10 <sup>-7</sup>
30	6(l) (free base)	2.15x10 <sup>-7</sup>
	6(o) (2HCl)	1.3x10 <sup>-7</sup>
	8 (2HCl)	8.9x10 <sup>-7</sup>
35	6(x) (2HCl)	2.7x10 <sup>-7</sup>
	11(a) (2HCl)	8.7x10 <sup>-7</sup>
	11(d) (HCl)	4.7x10 <sup>-8</sup>
40	11(e) (2HCl)	5.5x10 <sup>-7</sup>

(2) Inhibitory effect on TXA<sub>2</sub> synthetase

## 45 Method

Male Wistar rats were starved overnight. Five hundreds microliter of heparinized (10U/mL) whole blood was collected from abdominal aorta using polyethylene syringe (needle: 22 or 26G). The blood freshly drawn from animal was preincubated with 5  $\mu$ L of test compound at 37 °C. Five minutes later, 2.5  $\mu$ L of 6 mM of Ca ionophore A23187 (final concentration of 30  $\mu$ M) was added into tube, and incubation mixture was further incubated for 15 min. The reaction was terminated by centrifugation of tubes at 12,000 rpm for 2 min. TXB<sub>2</sub> content in the supernatant was determined by EIA as follows.

One milliliter of 0.5 M glycine-HCl buffer (pH 3.2) was added to 100  $\mu$ L of sample. The samples were mixed well and centrifuged at 1,700 G for 10 min at 4 °C. The extracted supernatant was applied to a SEP-PAK (registered Trade Mark) C<sub>18</sub> cartridge (Waters Assoc.). After washing with 10 mL of distilled water followed by 10 mL each of 15% ethanol and petroleum ether, the sample was eluted with 3 mL of ethyl acetate. The ethyl acetate fraction was evaporated to dryness under gentle N<sub>2</sub> stream and the residue was dissolved in EIA buffer

(final volume of 1 mL) following the addition of 300  $\mu$ L of 0.01 M NaHCO<sub>3</sub>-NaOH buffer (pH 10.0). EIA for TXB<sub>2</sub> was carried out according to a legend attached to the kit (Chyman Chemical Co., Inc.). Overall recovery of TXB<sub>2</sub> in this extraction procedure was 90%. The IC<sub>50</sub> values (concentration that produced 50% inhibition of TXB<sub>2</sub> synthesis) for the compounds examined were determined from concentration-response curves.

5

## Result

Table 2: Inhibitory activity on TXA<sub>2</sub> synthetase

Compounds Example No.	Inhibitory activity IC <sub>50</sub> , (M)
3 (e) (free base)	5.8 x 10 <sup>-6</sup>
5 (free base)	2.2 x 10 <sup>-7</sup>
11(e) (2HCl salt)	1.77x10 <sup>-6</sup>
6(bb) (2HCl salt)	2.0x10 <sup>-7</sup>
6(kk) (2HCl salt)	3.6x10 <sup>-6</sup>
6(nn) (2HCl salt)	1.35x10 <sup>-6</sup>
18(a) (2HCl salt)	1.33x10 <sup>-6</sup>

On the other hand, it was confirmed that the acute toxicity of the compound of the present invention is very weak. Therefore, the compounds of the present invention may be considered to be sufficiently safe and suitable for pharmaceutical use.

## Application for Pharmaceuticals

For the purpose above described, the compounds, of the formula (I), of the present invention, pharmaceutically acceptable salts and acid addition salts thereof and hydrates thereof may be normally administered systemically or partially, usually by oral or parenteral administration.

The doses to be administered are determined depending upon age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment etc. In the human adult, the doses per person are generally between 1 mg and 1000 mg, by oral administration, up to several times per day, and between 1 mg and 100 mg, by parenteral administration up to several times per day, or continuous administration between 1 and 24 hrs. per day intravenously.

As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

Administration of the compounds of the present invention, may be as solid compositions, liquid compositions or other compositions for oral administration, as injections, liniments or suppositories etc. for parenteral administration.

Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules. Capsules include hard capsules and soft capsules.

In such compositions, one or more of the active compound(s) is or are, admixed with at least one inert diluent (such as lactose, mannitol, glucose, hydroxypropyl cellulose, micro crystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate etc.) The compositions may also comprise, as is normal practice, additional substances other than inert diluents: e.g. lubricating agents (such as magnesium stearate etc.), disintegrating agents (such as cellulose calcium glycolate etc.), stabilizing agents (such as lactose etc.), and assisting agents for dissolving (such as glutamic acid, aspartic acid etc.).

The tablets or pills may, if desired, be coated with film of gastric or enteric material (such as sugar, gelatin, hydroxypropyl cellulose or hydroxypropylmethyl cellulose phthalate etc.), or be coated with more than two films. And further, coating may include containment within capsules of absorbable materials such as gelatin.

Liquid compositions for oral administration include pharmaceutically-acceptable solutions, emulsions, suspensions, syrups and elixirs.

In such compositions, one or more of the active compound(s) is or are comprise in inert diluent(s) commonly used in the art (purified water, ethanol etc.).

Besides inert diluents, such compositions may also comprise adjuvants (such as wetting agents, suspending agents etc.), sweetening agents, flavouring agents, perfuming agents and preserving agents.

Other compositions for oral administration include spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s).

5 Spray compositions may comprise additional substances other than inert diluents: e.g. stabilizing agents (sodium sulfite etc.), isotonic buffer (sodium chloride, sodium citrate, citric acid etc.)

For preparation of such spray compositions, for example, the method described in the United States Patent No. 2,868,691 or 3,095,355 (herein incorporated in their entirieties by reference) may be used.

10 Injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. In such compositions, one or more of active compound(s) is or are admixed with at least one of inert aqueous diluent(s) (distilled water for injection, physiological salt solution etc.) or inert non-aqueous diluent(s) (propylene glycol, polyethylene glycol, olive oil, ethanol, POLYSOLBATE80 (registered trade mark) etc.).

15 Injections may comprise additional other than inert diluents: e.g. preserving agents, wetting agents, emulsifying agents, dispersing agents, stabilizing agent (lactose etc.), assisting agents such as assisting agents for dissolving (glutamic acid, aspartic acid etc.).

They may be sterilized for example, by filtration through a bacteria-retaining filter, by incorporation of sterilizing agents in the compositions or by irradiation. They also be manufactured in the form of sterile solid compositions, for example, by freeze-drying, and which can be dissolved in sterile water or some other sterile diluents for injection immediately before used.

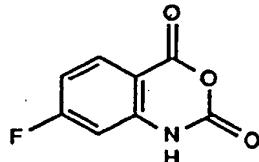
20 Other compositions for parenteral administration include liquids for external use, and endermic liniments (ointment etc.), suppositories and pessaries which comprise one or more of the active compound(s) and may be prepared by known methods.

#### Reference example and Examples

25 The following Reference examples and examples are intended to illustrate, but not limit, the present invention. In Reference examples and examples, "mp" shows "melting point".

#### Reference example 1

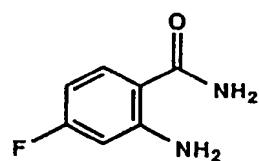
##### 4-fluoroisatoic anhydride



To a solution of 2-amino-4-fluorobenzoic acid (4.65 g) in 50 mL of mixed solvent (10 : 1 = toluene : tetrahydrofuran) was added phosgene (4.46 g, 1.93 M solution of toluene) dropwise via a drop funnel. The mixture was stirred at room temperature for 1 hour and then heated to reflux over night. The mixture was concentrated to about 10 mL and cooled in refrigerator. The precipitate was filtered, washed with ether (5 mL X 2) and air-dried to give the title compound (5.43 g) as a white solid having the following physical data.  
NMR (200MHz, DMSO-d6): δ 6.92 (dd, 1H), 7.11 (td, 1H), 8.00 (dd, 1H), 11.92 (broad, 1H).

#### Reference example 2

##### 4-fluoroanthranilamide



A solution of the isatoic anhydride compound (3.62 g, prepared in Reference example 1) in 100 mL of tetrahydrofuran was placed in a 200 mL round bottle equipped with gas in- and outlet. The anhydrous ammonia gas was gently bubbled into the solution for 1.5 to 2 hours. After removal of the solvent the residue was taken up in methylene chloride (30 mL) and water (30 mL). The precipitate was collected by filtration and washed with methylene chloride (10 mL) to give the title compound (1.95 g) as a pale white solid having the following physical data.

NMR (200MHz, DMSO-d<sub>6</sub>): δ 6.70 (m, 1H), 6.82 (m, 1H), 6.90 (broad, 2H), 7.72 (m, 1H).

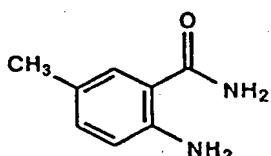
The following compounds were obtained by the same procedure as Reference example 1 and Reference example 2, by using the corresponding substituted anthranilic acid compound.

10

Reference example 2(a)

5-methylantranilamide

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The product was collected by filtration as a pale solid.

NMR (200MHz, DMSO-d<sub>6</sub>): δ 2.24 (s, 3H), 5.50 (broad, 2H), 6.62 (d, 1H), 7.07 (dd, 1H), 7.16 (d, 1H).

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Reference example 2(b)

5-chloroanthranilamide

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The product was collected by filtration as a pale solid.

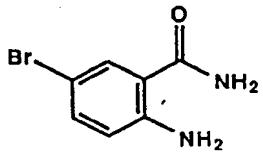
NMR (200MHz, DMSO-d<sub>6</sub>): δ 5.68 (broad, 2H), 6.64 (d, 1H), 7.20 (dd, 1H), 7.35 (d, 1H).

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Reference example 2(c)

5-bromoanthranilamide

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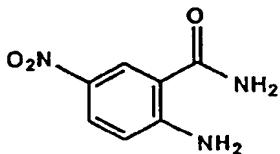
The product was collected by filtration as a pale brown.

NMR (200MHz, DMSO-d<sub>6</sub>): δ 6.66 (dd, 1H) 6.72 (broad, 2H), 7.20 (broad, 1H), 7.26 (dt, 1H), 7.70 (t, 1H), 7.82 (broad, 1H).

55

Reference example 2(d)

5-nitroanthranilamide

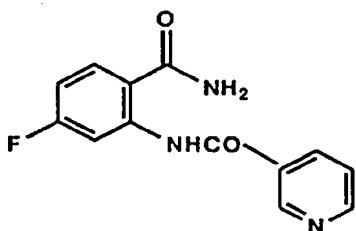


The product was collected by filtration as a solid.

10 NMR (200MHz, DMSO-d6): δ 6.80 (dd, 1H), 7.40 (broad, 1H), 7.90 (broad, 2H), 8.03 (dt, 1H), 8.20 (broad, 1H),  
8.56 (t, 1H).

Reference example 3

15 4-fluoro-2-[N-(3-pyridylcarbonyl)amino]benzamide

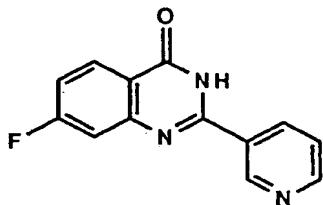


25 To a solution of the anthranilamide compound (1.54 g, prepared in Reference example 2) and triethylamine (1.4 g) in 100 mL of tetrahydrofuran was added nicotinoyl chloride hydrochloride (1.95 g). The resulting mixture was heated to reflux for one to three days and then concentrated. The residue was taken up in water (25 mL) and chloroform (30 mL). The insoluble crude product was collected by filtration and then vacuum dried. The  
30 crude product was triturated with 10 mL of ether and pentane solution (1:1) to afford the title compound (2.27 g) as a white solid having the following physical data.

NMR (200MHz, DMSO-d6): δ 7.10 (td, 1H), 7.80 (m, 1H), 7.99 (broad, 1H), 8.07 (m, 1H), 8.40-8.55 (m, 3H),  
8.90 (m, 1H), 9.15 (m, 1H).

35 Reference example 4

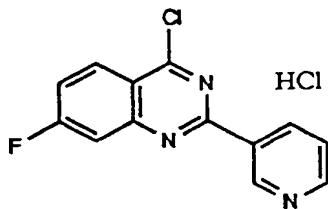
7-fluoro-2-(3-pyridyl)quinazolin-4-one



To a suspension of the benzamide compound (1.6 g, prepared in Reference example 3) in 60 mL of toluene  
50 was added sodium methoxide (853 mg). The solution was heated to reflux for one to three days. After cooling to room temperature, the mixture was quenched with ammonium chloride solution (30 mL) with a vigorously shaking. The mixture was cooled in refrigerator and the insoluble product was collected by filtration and dried in vacuum to give the title compound (1.39 g) as a white solid having the following physical data.  
NMR (200MHz, DMSO-d6): δ 7.43 (td, 1H), 7.53-7.64 (m, 2H), 8.20-8.28 (m, 1H), 8.50 (dt, 1H), 8.78 (dd, 1H),  
9.29 (m, 1H).

55 Reference example 5

4-chloro-7-fluoro-2-(3-pyridyl)quinazoline hydrochloride



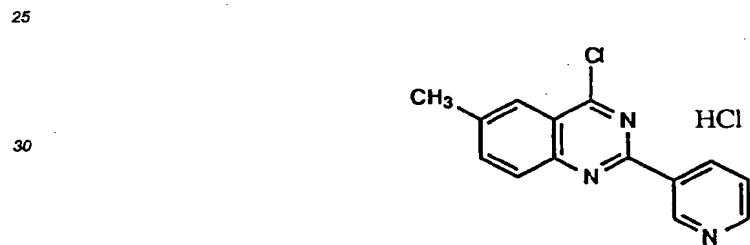
10 A suspension of the quinazolinone compound (1.2 g, prepared in Reference example 4) in 20 mL of thionyl chloride was heated to reflux for three hours. The excess of thionyl chloride was removed by distillation. The residue was distilled azeotropically with benzene (5 mL X 3) and then reduced the total volume to about 5 mL. After cooling in refrigerator, precipitate was collected by filtration and washed with benzene twice to give the title compound (1.38 g) as a crystalline solid having the following physical data.

15 NMR (200MHz, DMSO-d6):  $\delta$  7.80-7.95 (m, 2H), 8.07 (dd, 1H), 8.43-8.49 (m, 1H), 8.95 (d, 1H), 9.06 (dt, 1H), 9.65 (m, 1H).

20 The following compounds were obtained by the same procedure as Reference example 3→ Reference example 4→ Reference example 5, by using the anthranilamide compound prepared in Reference example 2(a), 2(b) or 2(c), or being on sale, and the corresponding acid chloride.

Reference example 5(a)

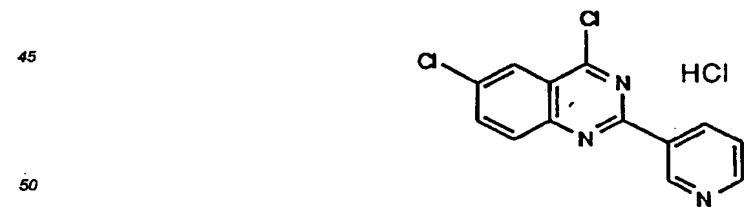
4-chloro-6-methyl-2-(3-pyridyl)quinazoline hydrochloride



35 The product was collected by filtration as a white solid.  
NMR (200MHz, DMSO-d6):  $\delta$  2.62 (s, 3H), 7.96-8.14 (m, 4H), 8.98 (d, 1H), 9.16 (d, 1H), 9.63 (m, 1H).

Reference example 5(b)

4,6-dichloro-2-(3-pyridyl)quinazoline hydrochloride



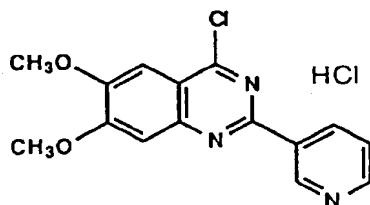
The product was collected by filtration as a white solid.  
mp : 210-214 °C.  
55 NMR (CDCl<sub>3</sub>):  $\delta$  7.28-8.17 (m, 3H), 8.35 (m, 1H), 8.89 (dd, 1H), 9.55 (dt, 1H), 9.98 (d, 1H).

Reference example 5(c)

4-chloro-6,7-dimethoxy-2-(3-pyridyl)quinazoline hydrochloride

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The product was collected by filtration as a white solid.

NMR (200MHz, DMSO-d6): δ 4.04 (s, 3H), 4.06 (s, 3H), 7.46 (s, 1H), 7.56 (s, 1H), 7.95 (m, 1H), 8.93 (d, 1H), 9.09 (d, 1H), 9.60 (m, 1H).

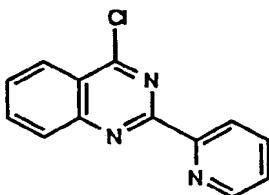
20

Reference example 5(d)

4-chloro-2-(2-pyridyl)quinazoline

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The product was collected by filtration as a light brown powder.

mp : 120-121 °C

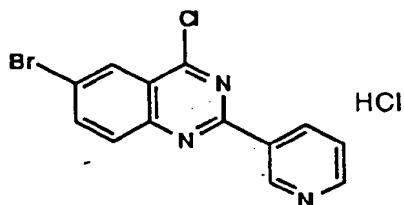
35

Reference example 5(e)

6-bromo-4-chloro-2-(3-pyridyl)quinazoline hydrochloride

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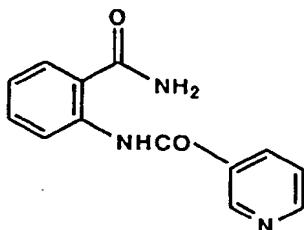
50

NMR (200MHz, DMSO-d6): δ 8.02 (m, 1H) 8.14 (dd, 1H), 8.33 (dt, 1H), 8.50 (t, 1H), 9.01 (d, 1H), 9.14(d, 1H), 9.64 (t, 1H).

55

Reference example 6

2-[N-(3-pyridylcarbonyl)amino]benzamide



10

To a solution of anthranilamide (8.2 g, being on sale) and triethylamine (18.0 g) in 100 mL of tetrahydrofuran/methylene chloride (1:1), was added nicotinoyl chloride hydrochloride (10.8 g). The mixture was allowed to stir at room temperature, under nitrogen atmosphere, for six hours. The solution was then concentrated under reduced pressure. The concentrate was taken up in ethyl acetate and water and the mixture filtered. The solid material was triturated in ether and filtered to give the title compound (11.5 g) as a yellow powder having the following physical data.  
mp : 220-222 °C.

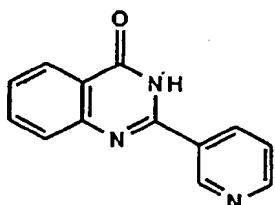
15

Reference example 7

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## 2-(3-pyridyl)quinazolin-4-one

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30

To a solution of the benzamide compound (11.5 g, prepared in Reference example 6) in 100 mL of toluene was added 95% sodium methoxide (5.7 g). The solution was heated at 60-80° C for three hours under nitrogen atmosphere. After cooling to room temperature, the solution was diluted with ammonium chloride solution. After stirring for one-half hour, the mixture was filtered. An NMR of the filtered material indicated the reaction was incomplete. The material was taken up in toluene and ethanol and 95% sodium methoxide (5.7 g) was added. The resulting solution was heated to reflux and stirred via a mechanical stirrer, under nitrogen atmosphere, overnight. The solvent had evaporated and the concentrate in the flask was collected and washed with ammonium chloride solution and methylene chloride. The solid material was collected by filtration and allowed to dry to give the title compound as a gray powder having the following physical data.  
mp : 275-276 °C.

35

NMR (200MHz, DMSO-d6): δ 7.50-7.61 (m, 2H), 7.75-7.90 (m, 2), 8.16 (d, 1H), 8.49 (m, 1H), 8.77 (d, 1H), 9.31 (s, 1H).

IR (KBr): ν 3185 (w), 3045 (m), 2915 (w), 1677 (s), 1603 (m), 1558 (w), 1474 (m), 769 (m) cm<sup>-1</sup>.

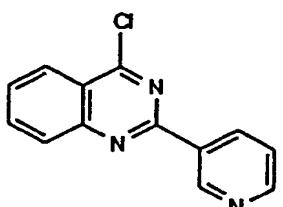
40

Reference example 8

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## 4-chloro-2-(3-pyridyl)quinazoline

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5 A solution of the quinazolinone compound (6.7 g, prepared in Reference example 7) and 5.7 mL of N,N-dimethylaniline in 200 mL of benzene was heated to reflux, under nitrogen atmosphere, for one-half hour with the removal of 15 mL of distillate. After cooling to room temperature, phosphorus oxychloride (4.5 g) was added and the resulting solution heated to reflux for six hours. After cooling to room temperature, the solution was washed with ice water and dilute sodium hydroxide solution. The organic extract was dried over sodium sulfate and concentrated under reduced pressure. The concentrate was triturated in ether and collected to give the title compound (3.0 g) having the following physical data.

mp : 178-179 °C.

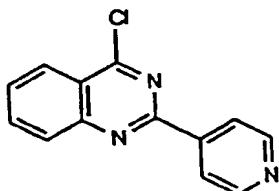
10 The following compounds were obtained by the same procedure as Reference example 6→ Reference example 7→ Reference example 8, by using anthranilamide and the corresponding acid chloride.

Reference example 8(a)

4-chloro-2-(4-pyridyl)quinazoline

15

20



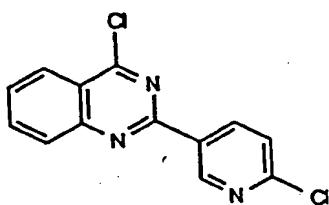
25 The product was collected by filtration as a brown solid.  
mp : 158-160 °C

Reference example 8(b)

30 4-chloro-2-(2-chloro-5-pyridyl)quinazoline

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40



NMR (CDCl<sub>3</sub>): δ 7.47 (d, 1H), 7.73 (t, 1H), 7.95 (t, 1H), 8.05-8.32 (m, 2H), 8.81 (dd, 1H) 9.55 (ds, 1H).

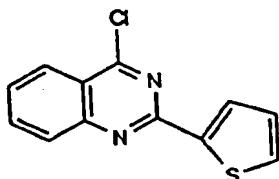
Reference example 8(c)

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4-chloro-2-(2-thienyl)quinazoline

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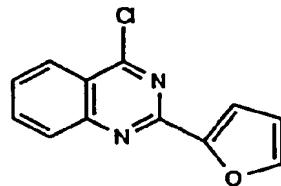
The product was collected by filtration as a tan powder.  
mp : 121-124 °C

Reference example 8(d)

4-chloro-2-(2-furyl)quinazoline

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The product was collected by the filtration as a tan powder.

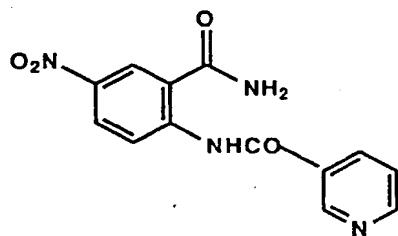
mp : 116-119 °C

20

Reference example 9

5-nitro-2-[N-(3-pyridylcarbonyl)amino]benzamide

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The title compound was obtained by the same procedure as Reference example 3, by using 5-nitroanthranilamide (prepared in Reference example 2 (d)).

The product was collected by filtration as a white solid.

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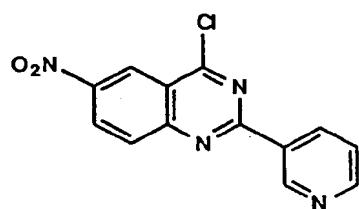
NMR (200MHz, DMSO-d<sub>6</sub>): δ 7.70 (m, 1H), 8.20 (broad, 1H), 8.35 (dt, 1H), 8.49 (dd, 1H), 8.85-8.92 (m, 3H), 9.15 (t, 1H).

40

Reference example 10

4-chloro-6-nitro-2-(3-pyridyl)quinazoline

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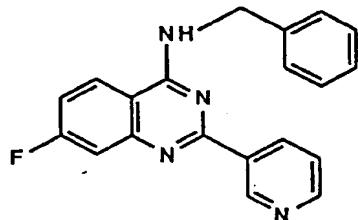
A suspension of the benzamide compound (0.925 g, prepared in Reference example 9) in phosphorous oxychloride (6 mL) was heated to reflux for 16 hours. After cooling to room temperature, the mixture was diluted by chloroform (30 mL) and then poured into 30 mL of ice-water mixture. The mixture was cooled in ice bath and carefully neutralized to pH 8 with a temperature control under 10 °C. The aqueous layer was extracted with chloroform (50 mL X 3). Combined organic layers were dried over with potassium carbonate and concentrated under reduced pressure to give the title compound (0.8 g) having the following physical data.

55

NMR (CDCl<sub>3</sub>): δ 7.27-7.35 (m, 2H), 7.52 (dd, 1H), 8.46-8.63 (m, 3H), 8.87 (d, 1H), 9.42 (s, 1H).

Example 1

4-phenylmethylamino-7-fluoro-2-(3-pyridyl)quinazoline

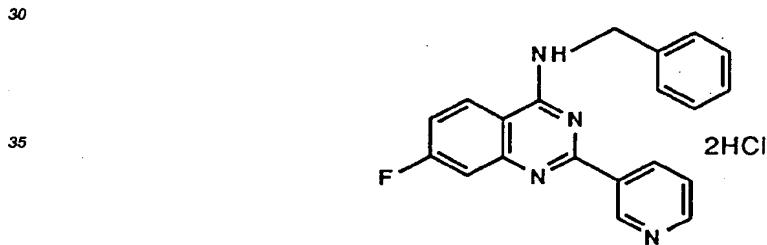


15 To a warm solution of the 4-chloroquinazoline compound (1.18 g, prepared in Reference example 5) in 50 mL ethanol was added phenylmethylamine (2.00 g). The mixture was heated to reflux for sixteen hours. The solution was then concentrated and the residue taken up in chloroform and ammonium chloride solution. The aqueous layer was extracted with chloroform (30 mL X 3) and dried over sodium sulfate. After concentration, the residue was triturated in pentane/ether solution to give the title compound (0.88 g) as a pale white solid  
20 having the following physical data.

mp : 199-203 °C.  
NMR ( $\text{CDCl}_3$ ):  $\delta$  5.00 (d, 2H), 6.01 (broad, 1H), 7.20 (td, 1H), 7.25-7.50 (m, 6H), 7.55 (dd, 1H), 7.70-7.77 (m, 1H), 8.70 (dd, 1H), 8.79 (dt, 1H), 9.74 (m, 1H).  
IR (KBr):  $\nu$  697 (s), 775 (s), 1166 (m), 1259 (m), 1341 (s), 1375 (s), 1444 (s), 1535 (s), 1592 (s), 1626 (s), 3135 (m), 3250 (m)  $\text{cm}^{-1}$ .

Example 2

4-phenylmethylamino-7-fluoro-2-(3-pyridyl)quinazoline dihydrochloride



40 To a suspension of the free base (0.70 g, prepared in Example 1) in 10 ml methanol was added excess amount of HCl in methanol. The mixture was stirred at room temperature for a half of an hour. The solvent was removed and the residue was triturated in ether (30 ml). The title compound (0.84 g) as a white powder having the following physical data, was obtained after filtration.

45 mp : 250 °C.  
NMR ( $\text{CDCl}_3$ ):  $\delta$  4.50 (d, 2H), 7.25-7.40 (m, 3H), 7.49-7.53 (m, 2H), 7.64 (dt, 1H), 7.82 (dd, 1H), 7.99 (m, 1H), 8.67 (m, 1H), 8.97 (dd, 1H), 9.15 (dd, 1H), 9.60 (d, 1H), 10.18 (broad, 1H).  
IR (KBr):  $\nu$  704 (m), 1266 (m), 1457 (s), 1574 (s), 1632 (s), 2920-2440 (broad, s), 3115 (broad, s)  $\text{cm}^{-1}$ .

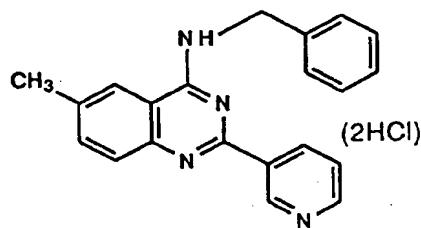
Example 3

50 The following compounds were obtained by the same procedure as Example 1, or Example 1 and Example 2, by using the corresponding 4-chloroquinazoline compound prepared by Reference example 5, 5(a) to 5(e) or Reference example 8, 8(a) to 8(d) and the proper amine.

Example 3(a)

4-phenylmethylamino-6-methyl-2-(3-pyridyl)quinazoline and its salt

EP 0 579 496 A1



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**(free base)**

The product was collected by filtration as a white solid.

mp : 179-180 °C (dec.).

NMR ( $\text{CDCl}_3$ ):  $\delta$  5.03 (d, 2H), 5.97 (broad, 1H), 7.28-7.53 (m, 7H), 7.61 (dd, 1H), 7.86 (d, 1H), 8.69 (dd, 1H),

15

8.80 (dt, 1H), 9.76 (m, 1H).

IR (KBr):  $\nu$  699 (w), 1365 (m), 1407 (w), 1437 (w), 1535 (s), 1569 (s), 1591 (s), 3200 (m)  $\text{cm}^{-1}$ .

**(2HCl salt)**

The product was collected by filtration as a white powder.

mp : 265-269 °C (dec.).

20

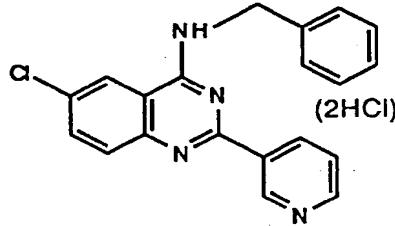
NMR ( $\text{CDCl}_3$ ):  $\delta$  2.50 (s, 3H), 5.03 (d, 2H), 7.28-7.42 (m, 3H), 7.48-7.53 (m, 2H), 7.80-7.91 (m, 2H), 8.06 (d, 1H), 8.45 (s, 1H), 8.91-9.00 (m, 2H), 9.55 (m, 1H).

IR (KBr):  $\nu$  704 (w), 1388 (m), 1568 (s), 1593 (s), 1617 (s), 2400-3100 (broad, s), 3200 (m), 3410 (broad, m)  $\text{cm}^{-1}$ .

25

**Example 3(b)**

4-phenylmethylamino-6-chloro-2-(3-pyridyl)quinazoline and its salt



**(free base)**

40

The product was purified by column chromatography.

mp : 240 °C.

NMR ( $\text{CDCl}_3$ ):  $\delta$  5.00 (d, 2H), 5.92 (broad, 1H), 7.32-7.51 (m, 6H), 7.71 (m, 2H), 7.90 (d, 1H), 8.71 (dd, 1H), 8.79 (dt, 1H), 9.75 (d, 1H).

IR (KBr):  $\nu$  697 (m), 1368 (s), 1419 (m), 1439 (m), 1534 (s), 1568 (s), 1590 (s), 3260 (w)  $\text{cm}^{-1}$ .

45

**(2HCl salt)**

The product was collected by filtration as a white powder.

mp : 255 °C (dec.).

NMR ( $\text{CDCl}_3$ ):  $\delta$  4.99 (d, 2H), 7.25-7.42 (m, 3H), 7.45-7.55 (m, 2H), 7.96-8.10 (m, 3H), 8.72 (m, 1H), 8.96 (d, 1H), 9.15 (d, 1H), 9.60 (m, 1H).

50

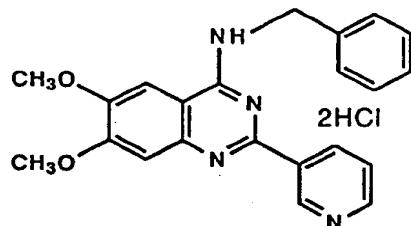
IR (KBr):  $\nu$  671 (w), 709 (m), 1356 (m), 1387 (s), 1457 (m), 1488 (m), 1518 (m), 1569 (s), 1608 (s), 1631 (s), 2335-2890 (broad, s), 3825 (s), 3230 (m), 3425 (m)  $\text{cm}^{-1}$ .

**Example 3(c)**

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4-phenylmethylamino-6,7-dimethoxy-2-(3-pyridyl)quinazoline and its salt

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## (free base)

The product was collected by filtration as a white solid.

mp : 193-196 °C.

15

NMR (200MHz, DMSO-d6): δ 3.92 (s, 3H), 3.94 (s, 3H), 4.92 (d, 2H), 6.90 (broad, 1H), 7.23-7.38 (m, 4H), 7.46-

7.55 (m, 3H), 7.76 (s, 1H), 8.62-8.78 (m, 3H), 9.52 (m, 1H).

IR (KBr): ν 698 (m), 850 (m), 1026 (m), 1131 (m), 1183 (m), 1213 (s), 1243 (s), 1366 (s), 1450 (s), 1501 (s), 1528 (s), 1591 (s), 1622 (m), 3270 (w) cm<sup>-1</sup>.

(2HCl salt)

20

The product was collected by filtration as a white solid.

mp : 240 °C (dec.).

NMR (200MHz, DMSO-d6): δ 3.98 (s, 6H), 5.01-5.06 (m, 2H), 7.25-7.41 (m, 3H), 7.74 (s, 1H), 7.85 (m, 1H), 8.14 (s, 1H), 8.90-8.95 (m, 2H), 9.56 (m, 1H).

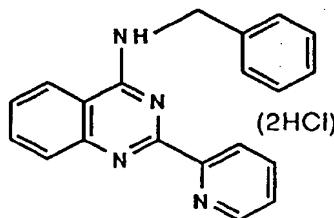
IR (KBr): ν 1243 (w), 1287 (s), 1378 (m), 1473 (m), 1504 (s), 1542 (m), 1596 (m), 1634 (s), 2400-3200 (broad, s), 3440 (broad, s) cm<sup>-1</sup>.

25

Example 3(d)

## 4-phenylmethylamino-2-(2-pyridyl)quinazoline and its salt

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35

## (free base):

The product was collected by filtration as a tan solid.

mp : 165-169 °C

(2HCl salt)

40

mp : 140-155 °C

NMR (200MHz, DMSO-d6): δ 5.12 (d, 2H), 7.35 (m, 3H), 7.58 (d, 2H), 7.83 (qd, 2H), 8.07 (t, 1H), 8.19-8.36

(m, 2H), 8.64 (d, 1H), 8.82 (d, 1H), 8.93 (d, 1H), 11.40 (t, 1H).

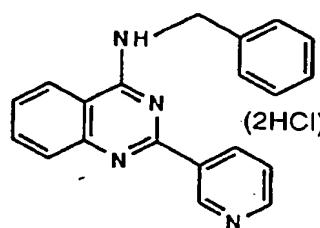
IR (KBr): ν 3370 (m), 3220 (m), 3200-2700 (m), 1625 (s), 1562 (s), 1524 (m), 1466 (m), 1385 (m), 765 (m) cm<sup>-1</sup>.

50

Example 3(e)

## 4-phenylmethylamino-2-(3-pyridyl)quinazoline and its salt

55



10

(free base)

mp : 137-138 °C.

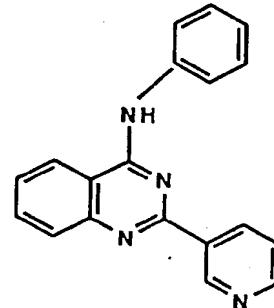
NMR ( $\text{CDCl}_3$ ):  $\delta$  5.01 (d, 2H), 6.20 (t, 1H), 7.26-7.49 (m, 6H), 7.71-7.79 (t, 3H), 7.95 (d, 1H), 8.68 (bs, 1H), 8.82 (d, 1H), 9.75 (bs, 1H).15 IR (KBr):  $\nu$  3305 (m), 1584 (s), 1520 (s), 1437 (m), 1410 (m), 1365 (s), 1325 (w), 765 (m), 694 (m)  $\text{cm}^{-1}$ .  
(2HCl salt)

mp : 225-235 °C

NMR (200MHz, DMSO-d6):  $\delta$  5.05 (d, 2H), 7.22-7.43 (m, 3H), 7.52 (m, 2H), 7.78 (t, 1H), 7.94-8.13 (m, 2H), 8.36 (s, 1H), 8.78 (d, 1H), 9.00 (dd, 1H), 9.12 (dd, 1H), 9.70 (s, 1H), 11.16 (broad t, 1H).20 IR (KBr):  $\nu$  3300-2615 (broad,s), 1629 (s), 1605 (s), 1569 (s), 1456 (m), 1384 (m), 763 (m), 705 (m)  $\text{cm}^{-1}$ .Example 3(f)

## 4-phenylamino-2-(3-pyridyl)quinazoline

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40 The product was collected by filtration as a yellow powder.  
mp : 173-178 °C.NMR (200MHz, DMSO-d6):  $\delta$  7.29 (t, 1H), 7.53 (t, 2H), 7.72-8.17 (m, 6H), 8.80 (d, 1H), 8.93 (d, 1H), 9.05 (d, 1H), 9.52 (s, 1H), 10.81 (bs, 1H).IR (KBr):  $\nu$  3160 (bw), 1559 (s), 1520(s), 1411 (m), 1363 (m), 754 (m)  $\text{cm}^{-1}$ .

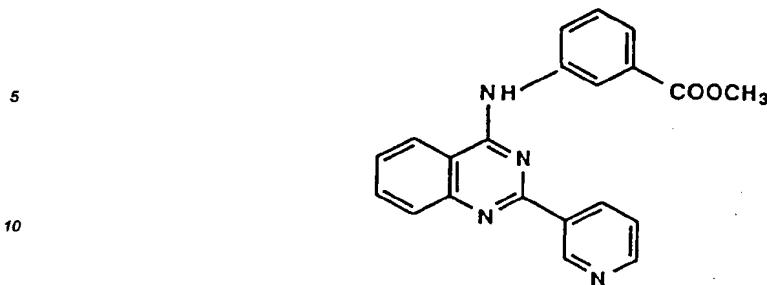
45

Example 3(g)

## 4-(3-methoxycarbonylphenyl)amino-2-(3-pyridyl)quinazoline

50

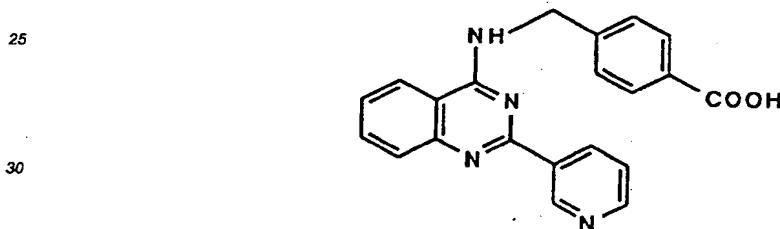
55



The product was collected by filtration as a yellow powder.  
 mp : 228-245 °C.  
 NMR (200MHz, DMSO-d6): δ 3.94 (s, 3H), 7.56-8.04 (m, 7H), 8.72-9.08 (m, 4H), 9.57 (s, 1H), 10.61 (bs, 1H).  
 IR (KBr): ν 3400 (bw), 1717(m), 1562 (s), 1520 (m), 1447 (m), 1374 (m), 1299 (m), 1278(m), 752 (m), 672 (w) cm<sup>-1</sup>.

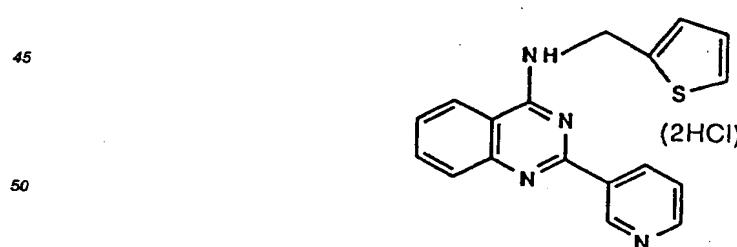
20 Example 3(h)

4-(4-carboxyphenylmethyl)amino-2-(3-pyridyl)quinazoline



mp : 285-294 °C  
 NMR (200MHz, DMSO-d6): δ 4.98 (d, 2H), 7.50-7.62 (m, 4H), 7.81 (d, 2H), 7.90 (d, 2H), 8.37 (d, 1H), 8.65 (m, 2H), 9.13 (t, 1H), 9.49 (s, 1H).  
 IR (KBr): ν 3340 (broad), 1747 (m), 1586 (s), 1531 (s), 1366 (m), 765 (m) cm<sup>-1</sup>.

40 Example 3(i)  
 4-(2-thienylmethyl)amino-2-(3-pyridyl)quinazoline and its salt



(free base)  
 55 mp : 195-197 °C  
 NMR (200MHz, DMSO-d6): δ 5.08 (d, 2H), 6.99 (m, 1H), 7.19 (m, 1H), 7.35 (dd, 1H), 7.55 (m, 2H), 8.30 (s, 1H), 8.69 (m, 1H), 8.83 (m, 1H), 9.13 (t, 1H).  
 IR (KBr): ν 3260 (bw), 1583 (s), 1525 (s), 1449 (m), 1359 (s), 763 (m), 747 (m), 720 (m) cm<sup>-1</sup>.

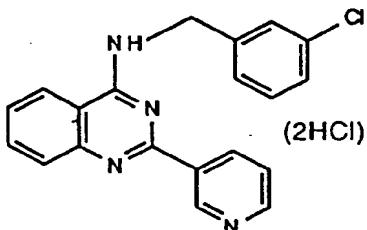
(2HCl salt)

mp : 255 °C (dec.).

NMR (200MHz, DMSO-d6): δ 5.20 (d, 2H), 7.01 (m, 1H), 7.22 (m, 1H), 7.43 (s, 1H), 7.77 (t, 1H), 8.00 (m, 3H), 8.21 (d, 1H), 8.61 (d, 1H), 8.99 (d, 1H), 9.23 (d, 1H), 9.74 (s, 1H), 10.45 (bs, 1H).

5 IR (KBr): ν 3405 (w), 3060-2615 (broad, m), 2363 (w), 1631(s), 1608 (s), 1570 (s), 1458 (m), 1387 (m), 773 (m), 712 (m) cm<sup>-1</sup>.Example 3(j)

10 4-(3-chlorophenylmethyl)amino-2-(3-pyridyl)quinazoline and its salt



(free base)

mp : 203-205 °C

NMR (200MHz, DMSO-d6): δ 4.92 (d, 2H), 7.27-7.61 (m, 6H), 7.82 (d, 2H), 8.33 (d, 1H), 8.66 (m, 2H), 9.08 (t, 1H), 9.53 (s, 1H).

25 IR (KBr): ν 3245 (w), 3050-2800 (w), 1586 (s), 1533 (m), 1436 (w), 1412 (w), 1366 (m), 765 (w) cm<sup>-1</sup>.

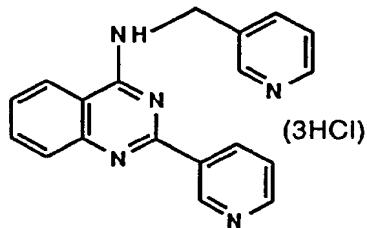
(2HCl salt)

mp : 235-250 °C

NMR (200MHz, DMSO-d6): δ 5.05 (d, 2H), 7.35 (m, 2H), 7.49 (m, 1H), 7.62 (s, 1H), 7.78 (t, 1H), 7.90-8.12 (m, 2H), 8.28 (s, 1H), 8.97 (m, 1H), 9.13 (dd, 1H), 9.66 (s, 1H), 10.97 (bs, 1H).

30 IR (KBr): ν 3035 (m), 2900-2700 (m), 1634 (m), 1610 (m), 1569 (m), 1387 (w), 780 (w), 710 (w) cm<sup>-1</sup>.Example 3(k)

35 4-(3-pyridylmethyl)amino-2-(3-pyridyl)quinazoline and its salt



(free base)

mp : 157-161 °C

NMR (200MHz, DMSO-d6): δ 4.95 (d, 2H), 7.33 (m, 1H), 7.55 (m, 2H), 7.85 (m, 3H), 8.33 (d, 1H), 8.46 (dd, 1H), 8.65-8.76 (m, 3H), 9.10 (t, 1H), 9.57 (s, 1H).

50 IR (KBr): ν 3255 (m), 3050-2900 (w), 1586 (s), 1533 (s), 1438 (m), 1368 (s), 763 (m), 700 (m) cm<sup>-1</sup>.

(3HCl salt)

mp : 240-257 °C

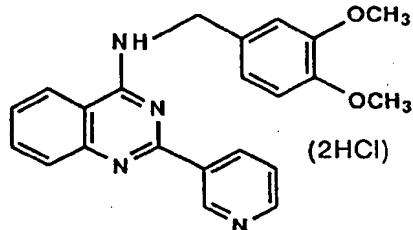
NMR (200MHz, DMSO-d6): δ 5.25 (d, 2H), 7.77 (t, 1H), 8.07 (m, 2H), 8.29 (d, 1H), 8.83 (m, 4H), 9.00 (d, 1H), 9.19 (m, 2H), 9.69 (s, 1H), 11.25 (bs, 1H).

55 IR (KBr): ν 3500 (w), 3100-2500 (broad, m), 1633 (s), 1611(s), 1569 (m), 1542 (m), 1457 (w), 790 (w), 720 (w) cm<sup>-1</sup>.

Example 3(l)

4-(3,4-dimethoxyphenylmethyl)amino-2-(3-pyridyl)quinazoline and its salt

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(free base)

mp : 155-159 °C

NMR (200MHz, DMSO-d6): δ 3.71 (d, 6H), 4.85 (d, 2H), 6.83-7.05 (m, 2H), 7.18 (s, 1H), 7.54 (m, 2H), 7.82 (d, 2H), 8.32 (d, 1H), 8.68 (dd, 1H), 8.77 (dd, 1H), 9.01 (t, 1H), 9.63 (s, 1H).

20

IR (KBr): ν 3395 (w), 3200-2900 (w), 1584 (s), 1514 (s), 1364 (m), 1263 (m), 1025 (m), 764 (w) cm<sup>-1</sup>.

(2HCl salt)

mp : 215-220 °C

NMR (200MHz, DMSO-d6): δ 3.70 (s, 6H), 4.97 (d, 2H), 6.90 (d, 1H), 7.02 (d, 1H), 7.24 (s, 1H), 7.77 (t, 1H), 7.92 (m, 1H), 8.04 (t, 1H), 8.73 (d, 1H), 8.97 (d, 1H), 9.16 (dd, 1H), 9.70 (s, 1H), 10.94 (bs, 1H).

25

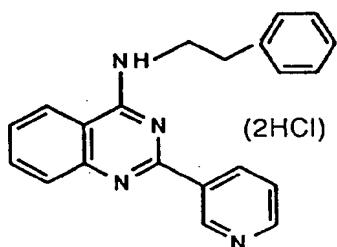
IR (KBr): ν 3404 (m), 3200-2300 (m), 1631 (s), 1610 (s), 1569 (s), 1514 (s), 1264 (m), 765 (m) cm<sup>-1</sup>.

25

Example 3(m)

4-phenylethylamino-2-(3-pyridyl)quinazoline and its salt

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35

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(free base)

mp : 136-139 °C

NMR (200MHz, DMSO-d6): δ 3.07 (t, 2H), 3.89 (q, 2H), 7.20-7.30 (m, 3H), 7.32 (d, 2H), 7.55 (m, 2H), 7.82 (s, 2H), 8.26 (s, 1H), 8.59 (t, 1H), 8.70 (m, 2H), 9.65 (s, 1H).

45

IR (KBr): ν 3290 (m), 3050-2900 (w), 1591 (s), 1514 (s), 1534 (s), 1442 (m), 1370 (s), 761 (m), 702 (m) cm<sup>-1</sup>.

(2HCl salt)

mp : 220-250°C (dec.).

NMR (200MHz, DMSO-d6): δ 3.11 (t, 2H), 4.05 (q, 2H), 7.15-7.38 (m, 5H), 7.77 (t, 1H), 8.01 (m, 2H), 8.35 (d, 1H), 8.70 (d, 1H), 9.01 (d, 1H), 9.15 (d, 1H), 9.69 (s, 1H), 10.68 (bs, 1H).

50

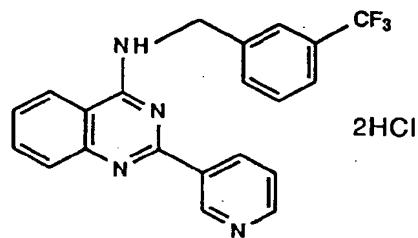
IR (KBr): ν 3400 (w), 3100-2500 (m), 1633 (s), 1613 (s), 1570 (m), 1457 (m), 1385 (m), 790 (w), 720 (w) cm<sup>-1</sup>.

55

Example 3(n)

4-(3-trifluoromethylphenylmethyl)amino-2-(3-pyridyl)quinazoline dihydrochloride

EP 0 579 496 A1

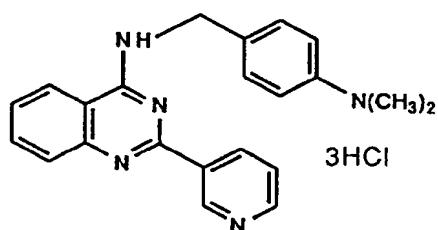


mp : >280 °C

NMR (200MHz, DMSO-d6): δ 5.14 (d, 2H), 7.52-8.35 (m, 8H), 8.70-9.20 (m, 3H), 9.67 (m, 1H).

Example 3(o)

15 4-(4-(N,N-dimethylamino)phenylmethylamino)-2-(3-pyridyl)quinazoline trihydrochloride

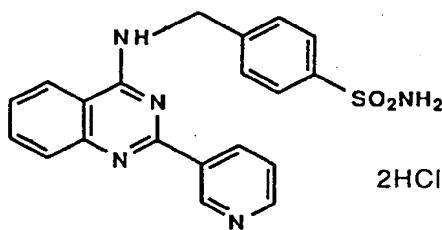


mp : 200-250 °C (dec.).

NMR (200MHz, DMSO-d6): δ 3.04 (s, 6H), 5.05 (d, 2H), 7.50-8.30 (m, 8H), 8.72 (s, 1H), 8.92-9.12 (m, 2H), 9.60 (m, 1H).

Example 3(p)

35 4-(4-sulfamoylphenylmethylamino)-2-(3-pyridyl)quinazoline dihydrochloride



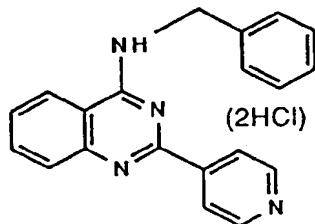
mp : 255-265 °C

NMR (200MHz, DMSO-d6): δ 5.10 (d, 2H), 7.32 (bs, 2H), 7.66-8.20 (m, 8H), 8.62 (d, 1H), 8.95 (m, 2H), 9.56 (ms, 1H).

50 Example 3(q)

4-phenylmethylamino-2-(4-pyridyl)quinazoline and its salt

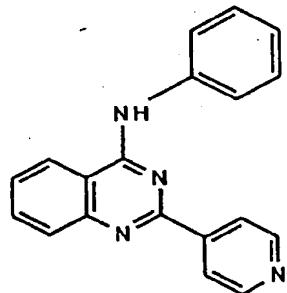
55



10 (free base)  
mp : 195-197 °C  
NMR (200MHz, DMSO-d<sub>6</sub>): δ 4.96 (d, 2H), 7.19-7.66 (m, 6H), 7.83 (d, 2H), 8.30 (d, 2H), 8.39 (d, 1H), 8.72 (d, 2H), 9.10 (t, 1H).  
15 IR (KBr): ν 3250 (w), 1585 (s), 1561(s), 1529 (s), 1411 (m), 1374 (s), 1325 (s), 768 (m), 702 (m) cm<sup>-1</sup>.  
(2HCl salt):  
mp : 260-270 °C  
NMR (200MHz, DMSO-d<sub>6</sub>): δ 5.02 (d, 2H), 7.22-7.40 (m, 3H), 7.51 (d, 2H), 7.75 (t, 1H), 8.00 (t, 1H), 8.16 (d, 1H), 8.66 (d, 1H), 8.81 (d, 2H), 9.06 (d, 2H), 10.32 (bs, 1H).  
20 IR (KBr): ν 3385 (m), 3210 (m), 3060-2600 (s), 1627 (s), 1604 (s), 1567 (s), 1505 (m), 1452 (m), 1383 (m), 760 (m), 709 (m) cm<sup>-1</sup>.

Example 3(r)

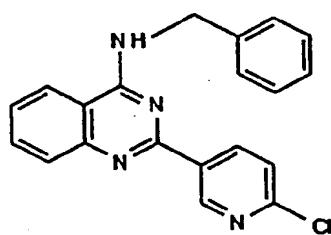
25 4-phenylamino-2-(4-pyridyl)quinazoline



40 mp : 270-274 °C  
NMR (200MHz, DMSO-d<sub>6</sub>): δ 7.22 (t, 1H), 7.70 (m, 1H), 7.94 (m, 4H), 8.37 (m, 2H), 8.68 (d, 1H), 8.82 (d, 2H), 10.13 (s, 1H).  
IR (KBr): ν 3270 (m), 3145 (m), 1620 (s), 1572 (s), 1524 (s), 1488 (s), 1443 (s), 1414 (s), 1374 (s), 749 (m), 702 (m) cm<sup>-1</sup>.

Example 3(s)

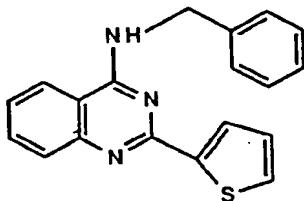
4-phenylmethylamino-2-(2-chloro-5-pyridyl)quinazoline



mp : 212-214 °C  
 NMR ( $\text{CDCl}_3$ ):  $\delta$  4.96 (d, 2H), 6.03 (bs, 1H), 7.20-7.55 (m, 7H), 7.66-7.95 (m, 3H), 8.78 (m, 1H), 9.52 (m, 1H).  
 IR (KBr):  $\nu$  3315 (w), 1580 (s), 1532 (ms), 1446 (mw), 1343 (m), 1269 (w)  $\text{cm}^{-1}$ .

5    Example 3(t)

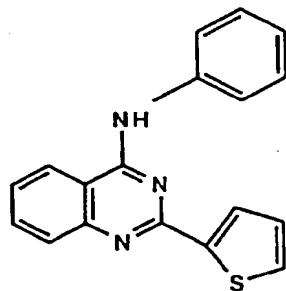
4-phenylmethylamino-2-(2-thienyl)quinazoline



mp : 158-163 °C  
 NMR (200MHz, DMSO-d6):  $\delta$  4.88 (d, 2H), 7.14-7.53 (m, 6H), 7.62-7.81 (m, 3H), 7.92 (m, 1H), 8.30 (d, 1H),  
 20 8.97 (t, 1H).  
 IR (KBr):  $\nu$  3305 (w), 1571 (s), 1519 (s), 1451(m), 1408 (m), 1377 (s), 769 (m), 730 (m), 737 (m)  $\text{cm}^{-1}$ .

Example 3(u)

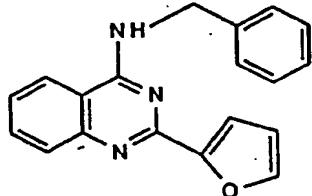
25    4-phenylamino-2-(2-thienyl)quinazoline



40    mp : 137-139 °C.  
 NMR (200MHz, DMSO-d6):  $\delta$  7.20 (m, 2H), 7.62-8.09 (m, 9H), 8.58 (d, 1H), 9.85 (s, 1H).  
 IR (KBr):  $\nu$  3430 (w), 1616 (w), 1662 (w), 1561 (s), 1461 (m), 1488 (m), 1461 (m), 1406 (m), 1374 (m), 749 (w)  
 $\text{cm}^{-1}$ .

45    Example 3(v)

4-phenylmethylamino-2-(2-furyl)quinazoline

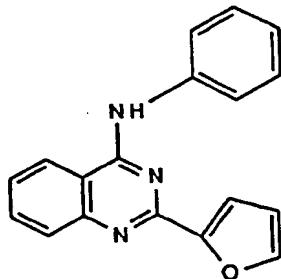


mp : 152-154 °C

NMR ( $\text{CDCl}_3$ ):  $\delta$  4.95 (d, 2H), 6.00 (t, 1H), 6.56 (m, 1H), 7.31-7.49 (m, 7H), 7.62-7.76 (m, 3H), 7.97 (d, 1H).  
 IR (KBr):  $\nu$  3290 (m), 1589 (m), 1531 (s), 1365 (s), 1015 (m), 890 (m), 762 (s)  $\text{cm}^{-1}$ .

Example 3(w)

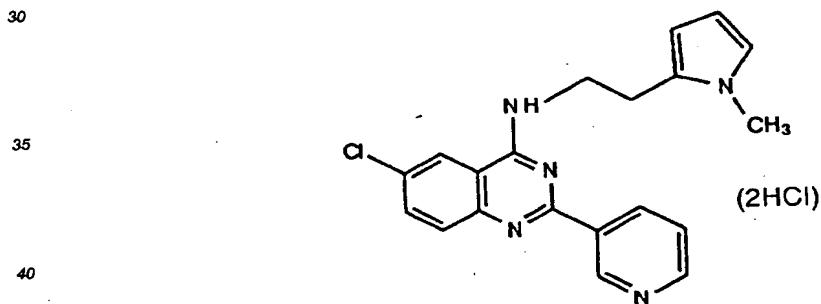
5 4-phenylamino-2-(2-furyl)quinazoline



20 mp : 183-184 °C  
 NMR ( $\text{CDCl}_3$ ):  $\delta$  6.58 (m, 1H), 7.13-7.37 (m, 2H), 7.39-7.58 (q, 4H), 7.65 (s, 1H), 7.72-7.94 (m, 4H), 8.03 (d, 1H).  
 IR (KBr):  $\nu$  3456 (w), 1607 (m), 1559 (s), 1524 (s), 1485 (s), 1446 (m), 1419 (m), 1360 (m), 748 (m)  $\text{cm}^{-1}$ .

Example 3(x)

25 6-chloro-4-(2-(1-methyl-2-pyrrolyl)ethyl)amino-2-(3-pyridyl)quinazoline and its salt



45 (free base)

The product was collected by filtration as a white solid.  
 NMR (200MHz, DMSO-d6):  $\delta$  2.99 (t, 2H), 3.58 (s, 3H), 3.89 (q, 2H), 5.90 (m, 2H), 6.62 (m, 1H), 7.55 (m, 1H), 7.83 (m, 2H), 8.44 (d, 1H), 8.70-8.75 (m, 3H), 9.61 (m, 1H).

(2HCl salt)

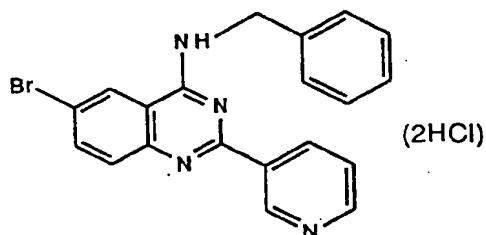
The product was collected by filtration as a white powder.

50 mp : 190-194 °C (dec.).

NMR (200MHz, DMSO-d6):  $\delta$  3.02 (t, 2H), 3.58 (s, 3H), 3.97 (q, 2H), 5.88 (m, 2H), 6.60 (t, 1H), 7.97-8.14 (m, 2H), 8.16 (d, 1H), 8.74 (d, 1H), 8.99 (dd, 1H), 9.16 (d, 1H), 9.63 (d, 1H), 10.00 (broad, 1H).  
 IR (KBr):  $\nu$  711 (w), 709 (m), 1359 (m), 1388 (s), 1438 (m), 1549 (s), 1570 (s), 1599 (s), 1634 (s), 2065 (m), 2365 (m), 2555 (s), 3110 (m), 3360 (m)  $\text{cm}^{-1}$ .

Example 3(y)

55 4-phenylimethylamino-6-bromo-2-(3-pyridyl)quinazoline and its salt



(free base)

The product was collected by filtration as a solid.

NMR (200MHz, DMSO-d<sub>6</sub>): δ 4.90 (d, 2H), 7.25-7.56 (m, 6H), 7.75 (d, 2H), 7.94 (dd, 1H), 8.66-8.71 (m, 3H),

9.18 (broad, 1H), 9.54 (d, 1H).

(2HCl salt)

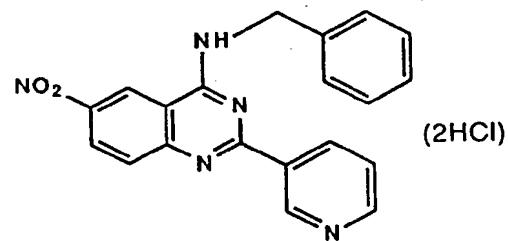
mp : 233-240 °C (dec.).

NMR (200MHz, DMSO-d<sub>6</sub>): δ 4.99 (d, 2H), 7.25-7.42 (m, 3H), 7.51-7.57 (m, 3H), 7.96-8.03 (m, 1H), 8.07-8.10

(m, 2H), 8.93-9.00 (m, 2H), 9.19 (d, 1H), 9.62 (d, 1H), 10.30 (broad, 1H).

20 IR (KBr): ν 701 (m), 1357 (m), 1404 (s), 1446 (m), 1519 (s), 1549 (s), 1628 (s), 2400-3000 (broad, s), 3140 (s) cm<sup>-1</sup>.Example 3(z)

25 4-phenylmethylamino-6-nitro-2-(3-pyridyl)quinazoline and its salt



(free base)

The product was collected by filtration as a solid.

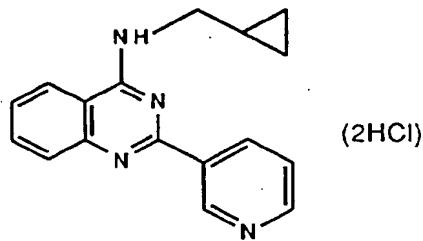
40 NMR (200MHz, DMSO-d<sub>6</sub>): δ 4.95 (d, 2H), 7.25-7.40 (m, 3H), 7.48-7.58 (m, 3H), 7.93 (dd, 1H), 8.50 (dt, 1H), 8.70-8.80 (m, 2H), 9.46 (d, 1H), 9.58 (d, 1H), 9.70 (broad, 1H).

(2HCl salt)

mp : 289-292 °C (dec.).

NMR (200MHz, DMSO-d<sub>6</sub>): δ 5.00 (d, 2H), 7.25-7.42 (m, 3H), 7.51-7.55 (m, 2H), 8.04-8.09 (m, 2H), 8.59 (dt, 1H), 9.00 (dd, 1H), 9.27 (d, 1H), 9.54 (d, 1H), 9.67 (s, 1H), 10.18 (broad, 1H).45 IR (KBr): ν 671 (m), 709 (m), 757 (m), 784 (m), 1349 (s), 1514 (s), 1578 (s), 1636 (s), 2445 (broad, s), 2860 (w), 3070 (m) cm<sup>-1</sup>.Example 3(aa)

50 4-(cyclopropylmethyl)amino-2-(3-pyridyl)quinazoline and its salt



(free base)

mp : 162-163 °C.

NMR (200MHz, DMSO-d<sub>6</sub>): δ 0.38 (m, 2H), 0.49 (m, 2H), 1.33 (m, 1H), 3.58 (t, 2H), 7.55 (m, 2H), 7.79 (m, 2H),

8.32 (d, 1H), 8.56 (t, 1H), 8.69 (m, 2H), 9.62 (s, 1H).

IR(KBr): ν 3265(w), 1537 (s), 1525 (s), 1437 (w), 1369 (s), 762 (m) cm<sup>-1</sup>.

(2HCl salt)

mp : 230-239 °C

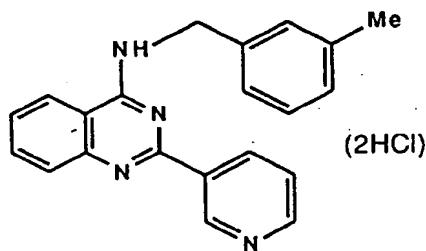
NMR (200MHz, DMSO-d<sub>6</sub>): δ 0.43 (m, 2H), 0.50 (m, 2H), 1.32 (m, 1H), 3.71 (t, 2H), 7.78 (t, 1H), 7.93 (m, 1H),

8.05 (t, 1H), 8.34 (d, 1H), 8.77 (d, 1H), 8.99 (d, 1H), 9.08 (dd, 1H), 9.68 (s, 1H), 10.68 (bs, 1H).

IR (KBr): ν 3405-2700 (broad, s), 2365 (w), 1632 (s), 1600 (s), 1570 (m), 1542 (m), 1458 (w), 1383 (m), 1321 (w), 767 (w), 669 (w) cm<sup>-1</sup>.Example 3(bb)

25

4-(3-methylphenylmethylamino)-2-(3-pyridyl)quinazoline and its salt



(free base)

mp : 166-169 °C.

NMR (200MHz, DMSO-d<sub>6</sub>): δ 2.28 (s, 3H), 4.90 (s, 2H), 7.03 (bd, 1H), 7.18-7.32 (m, 3H), 7.47-7.61 (m, 2H),

7.81 (d, 1H), 8.35 (d, 1H), 8.69 (m, 2H), 9.02 (bt, 1H), 9.58 (s, 1H).

IR (KBr): ν 3245 (m), 1567 (s), 1533 (s), 1438 (m), 1443 (m), 1368 (s), 1326 (m), 762 (m), 699 (m) cm<sup>-1</sup>.

(2HCl salt)

mp : 225-244 °C.

NMR (200MHz, DMSO-d<sub>6</sub>): δ 2.29 (s, 3H), 5.03 (s, 2H), 7.10 (d, 1H), 7.20-7.38 (m, 3H), 7.77 (t, 1H), 7.92-8.10

(m, 2H), 8.34 (d, 1H), 8.76 (d, 1H), 9.02 (d, 2H), 9.20 (d, 2H), 9.69 (s, 1H), 11.05 (bt, 1H).

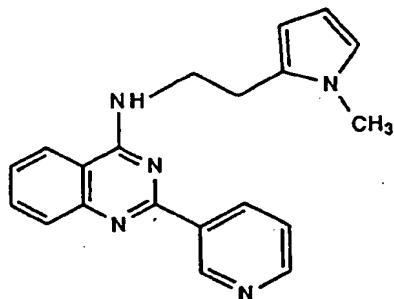
IR (KBr): ν 3400 (m), 3050-2600 (broad, m), 1627 (s), 1570 (s), 1542 (m), 1457 (m), 1385 (m), 770 (m), 680 (m) cm<sup>-1</sup>.

50

Example 3(cc)

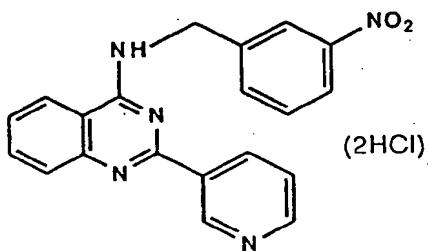
4-(2-(1-methyl-2-pyrrolyl)ethylamino)-2-(3-pyridyl)quinazoline

55



mp : 140-142 °C.  
 15 NMR (200MHz, DMSO-d6): δ 3.00 (t, 2H), 3.58 (s, 3H), 3.88 (qd, 2H), 5.91 (m, 2H), 6.63 (t, 1H), 7.53 (m, 2H),  
 7.80 (d, 2H), 8.24 (d, 1H), 8.59 (t, 1H), 8.66-8.79 (m, 2H), 9.62 (s, 1H).  
 IR (KBr): ν 3445 (m), 3130-2900 (w), 2369 (w), 1567 (s), 1514 (s), 1533 (s), 1443 (m), 1438 (m), 1368 (s), 1351  
 (m), 1187 (w), 762 (m), 699 (m) cm<sup>-1</sup>.

20 Example 3(dd)  
 4-(3-nitrophenylmethyl)amino-2-(3-pyridyl)quinazoline and its salt

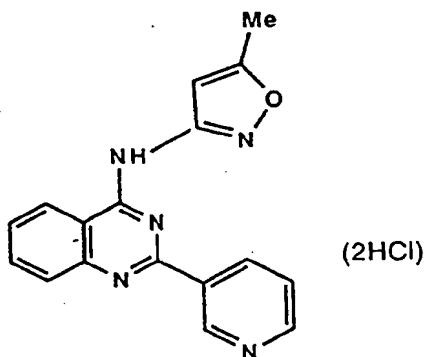


35 (free base)  
 mp : 218-220 °C.  
 NMR (200MHz, DMSO-d6): δ 5.05 (d, 2H), 7.46-7.69 (m, 3H), 7.83 (m, 2H), 7.84 (d, 1H), 8.13 (d, 1H), 8.37 (m,  
 2H), 8.67 (m, 2H), 9.18 (t, 1H), 9.52 (s, 1H).  
 (2HCl salt)  
 40 mp : 263-265 °C.  
 NMR (200MHz, DMSO-d6): δ 5.15 (d, 2H), 7.60-7.86 (m, 3H), 7.90-8.19 (m, 5H), 8.26 (d, 1H), 8.43 (s, 1H),  
 8.75 (d, 1H), 9.00 (d, 1H), 9.18 (d, 1H), 9.65 (s, 1H), 11.03 (bs, 1H).

45 Example 3(ee)  
 4-(5-methyl-3-isoxazolyl)amino-2-(3-pyridyl)quinazoline and its salt

50

55



15 (free base)  
NMR (200MHz, DMSO-d6):  $\delta$  2.28 (s, 3H), 7.64 (s, 1H), 7.52-7.71 (m, 2H), 7.95 (m, 2H), 8.72 (m, 4H), 9.68 (m, 1H), 10.98 (s, 1H).

20 (2HCl salt)  
mp : 228-230 °C.  
NMR (200MHz, DMSO-d6):  $\delta$  2.53 (s, 3H), 7.09 (s, 1H), 7.74 (m, 1H), 8.04 (m, 2H), 8.18 (m, 1H), 8.75 (d, 1H), 9.06 (d, 1H), 9.34 (d, 1H), 9.64 (s, 1H).

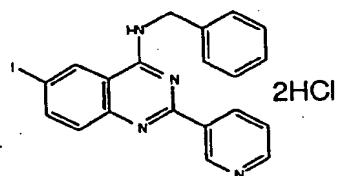
The following compounds were obtained by the same procedure as described in Reference examples 2, 3, 4 and 5 and examples 1 and 2 or in Reference example 6, 7 and 8 and examples 1 and 2, by using isatoic anhydride.

25

Example 3(ff)

6-iodo-4-phenylmethylamino-2-(3-pyridyl)quinazoline dihydrochloride

30

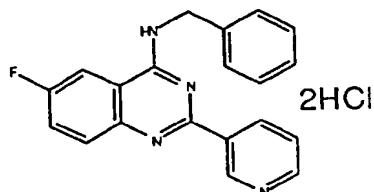


40 mp : 205-10 °C. (dec.)  
NMR (200MHz, DMSO-d6)  $\delta$ : 5.00 (d, 2H), 7.28-7.41 (m, 3H), 7.47-7.53 (m, 2H), 7.80 (d, 1H), 7.95 (m, 1H), 8.23 (dd, 1H), 8.92-8.98 (m, 2H), 9.08 (d, 1H), 9.59 (m, 1H), 10.00 (broad, 1H).

Example 3(gg)

45 6-fluoro-4-phenylmethylamino-2-(3-pyridyl)quinazoline dihydrochloride

50



mp : 200-2 °C. (dec.)

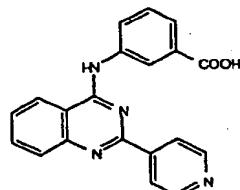
NMR (200MHz, DMSO-d<sub>6</sub>) δ: 5.02 (d, 2H), 7.28-7.41 (m, 3H), 7.51-7.54 (m, 2H), 7.82-8.02 (m, 2H), 8.07-8.20 (m, 1H), 8.40-8.52 (d, 1H), 8.97 (dd, 1H), 9.15 (d, 1H), 9.61 (s, 1H), 10.08 (broad, 1H).

Example 3(hh)

5

4-(3-carboxyphenyl)amino-2-(4-pyridyl)quinazoline

10



15

mp : >300°C

NMR (200MHz, DMSO-d<sub>6</sub>) δ: 7.65 (t, 1H), 7.78 (m, 2H), 7.99 (d, 2H), 8.22 (d, 1H), 8.68 (d, 2H), 8.75 (d, 1H), 8.87 (m, 3H), 10.44 (s, 1H).

20

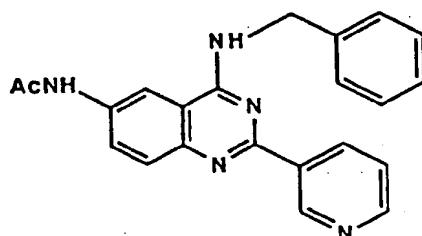
IR (KBr) v: 3370-2800 (w, broad), 1712 (m), 1632 (m), 1571 (s), 1545 (s), 1473 (m), 1437 (m), 1376 (m), 764 (m) cm<sup>-1</sup>.

25

Example 4

6-acetylamino-4-phenylmethylamino-2-(3-pyridyl)quinazoline

30



35

To warmed suspension of the nitroquinazoline compound (141 mg, prepared in Example 3(z)) in acetic acid (4 mL) was added zinc dust (80 mg). The red mixture was heated to reflux for overnight. After cooling down to room temperature the precipitate was removed by filtration. The filtrate was neutralized to pH 8 and extracted with chloroform. The insoluble solid was removed by filtration during the extraction. The chloroform was dried over potassium carbonate and then concentrated to 0.5 mL (total volume). The precipitate was collected by filtration to give the title compound (20 mg) having the following physical data.

45

mp : 127 °C (dec.).

NMR (200MHz, DMSO-d<sub>6</sub>): δ 2.12 (s, 3H), 4.88 (d, 2H), 7.22-7.37 (m, 3H), 7.45-7.53 (m, 2H), 7.75 (m, 1H),

8.32 (m, 2H), 8.58-8.69 (m, 3H), 8.94 (broad, 1H), 9.52 (m, 1H), 10.23 (broad, 1H).

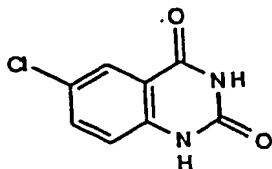
IR (KBr): v 700 (w), 840 (w), 1318 (m), 1368 (m), 1426 (m), 1537 (s), 1584 (s), 1676 (m), 3065 (m), 3365 (m) cm<sup>-1</sup>.

50

Reference example 11

6-chloro-(1H,3H)-quinazolin-2,4-dione

55

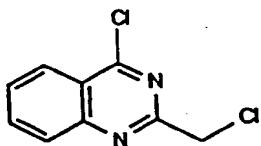


To a solution of 5-chloroanthranilamide (3.4 g) in tetrahydrofuran (50 mL) was added phosgene (16 mL, 1.93M solution in toluene) via an addition funnel. The reaction mixture was stirred at room temperature for 4 hours and then heated to reflux for another two hours. The reaction mixture was concentrated to a total volume about 10 mL. After cooling, the title compound (3.72 g) having the following physical data, was collected by filtration and dried in vacuum.

10 NMR (200MHz, DMSO-d<sub>6</sub>): δ 7.19 (d, 1H), 7.69 (dd, 1H), 7.82 (d, 1H), 11.28 (broad, 1H), 11.45 (broad, 1H).

15 Reference example 12

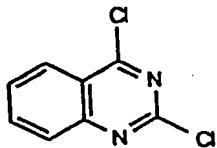
4-chloro-2-chloromethylquinazoline



25 To a solution of anthranilonitrile (11.8 g) and chloroacetonitrile (7.5 g) in 1,4-dioxane (200 mL), cooled in an ice bath, was bubbled HCl gas. The reaction mixture was stirred for two and one-half hours at which time the reaction was allowed to warm to room temperature and continued to bubble HCl gas for 16 hours. After the HCl gas bubbling was ceased, nitrogen gas was bubbled through to remove any unreacted HCl gas. The 30 mixture was concentrated at 45 °C in vacuo. The mixture was partitioned between methylene chloride (300 mL) and water (400 mL). The organic layer was separated, dried over anhydrous magnesium sulfate, and concentrated. The concentrate was dissolved in 200 mL of warm hexane, filtered and allowed to cool to room temperature. The title compound (9.1 g) was collected by filtration.

35 Reference example 13

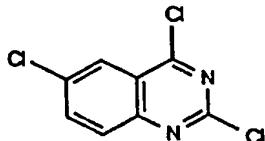
2,4-dichloroquinazoline



45 A mixture of benzoyleneurea (20.0 g), phosphorus oxychloride (100 mL) and N,N-dimethylaniline (12 mL) was refluxed for five hours. After stirring overnight at room temperature, the mixture was heated to reflux once more for an additional four hours. The cooled mixture was then poured into ice and the precipitate collected. The precipitate was purified on silica gel column with 5% methanol/chloroform as eluent. The isolated product 50 was triturated in ether/hexane and collected to obtain the title compound (6.9 g). The following compound was obtained by the same procedure as Reference example 13, by using 6-chloro-(1H,3H)-quinazolin-2,4-dione prepared by Reference example 11.

55 Reference example 13(a)

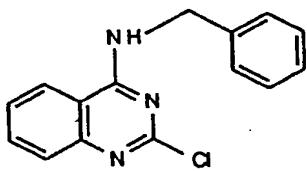
2,4,6-trichloroquinazoline



mp : 125 °C.  
NMR (200MHz, DMSO-d6): δ 8.09 (d, 1H), 8.21 (dd, 1H), 8.33 (d, 1H).

10  
Reference example 14

4-phenylmethylamino-2-chloroquinazoline

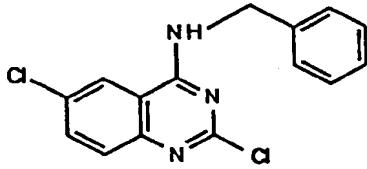


20  
The title compound having the following physical data, was obtained by the same procedure as Example 1, by using the dichloroquinazoline prepared in Reference example 13 and phenylmethylamine (equivalent to dichloroquinazoline).  
25 mp : 178-180 °C.  
NMR (CDCl<sub>3</sub>): δ 8.6 (d, 2H), 6.05 (s, 1H), 7.32-7.51 (m, 6H), 7.62-7.85 (m, 3H).

The following compounds were obtained by the same procedure as Reference example 14, by using the corresponding 4-chloro compounds prepared in Reference example 13(a) and 12, respectively.

30  
Reference example 14(a)

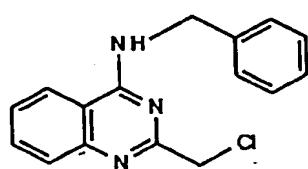
4-phenylmethylamino-2,6-dichloroquinazoline



40  
NMR (200MHz, DMSO-d6): δ 4.74 (d, 2H), 7.28-7.43 (m, 5H), 7.67 (d, 1H), 7.85 (dd, 1H), 8.50 (d, 1H), 9.36 (broad, 1H).

45  
Reference example 14(b)

4-phenyl methylamino-2-chloromethylquinazoline



55  
mp : 137-139 °C.

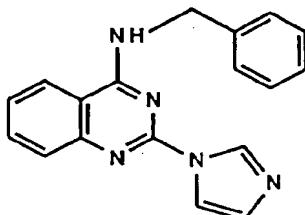
NMR ( $\text{CDCl}_3$ ):  $\delta$  4.68 (s, 2H), 4.90 (d, 2H), 6.00 (bs, 1H), 7.27-7.90 (m, 9H).

Example 5

5 4-phenylmethylamino-2-(1-imidazolyl)quinazoline

10

15



A mixture of the 2-chloro compound (0.81 g, prepared in Reference example 14), imidazole (0.81 g) and phenol (3.0 g) was heated to reflux for four and one-half hours. The mixture was then taken up in chloroform, washed twice with sodium hydroxide solution, dried over anhydrous potassium carbonate and concentrated. The concentrate was triturated in ether and collected to obtain the title compound (0.7 g) as a yellow solid having the following physical data.

mp : 212-214°C.

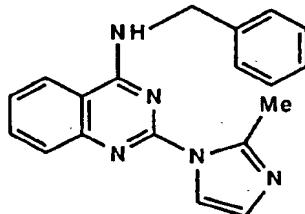
NMR ( $\text{CDCl}_3$ ):  $\delta$  4.86 (d, 2H), 6.05 (broad s, 1H), 7.32-7.51 (m, 6H), 7.62-7.85 (m, 3H).  
The following compounds were obtained by the same procedure as Example 5, by using 4-phenylmethylamino-2-chloroquinazoline prepared in Reference example 14, 14(a) and 14(b) or corresponding quinazoline, and the proper heterocyclic compounds.

Example 5(a)

30 4-phenylmethylamino-2-(2-methyl-1-imidazolyl)quinazoline

35

40



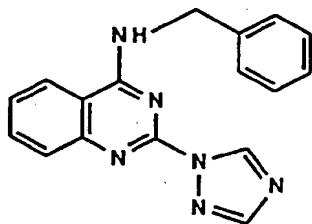
mp : 182-186 °C.

NMR ( $\text{CDCl}_3$ ):  $\delta$  2.89 (s, 3H), 4.92 (d, 2H), 6.30 (broad, 1H), 6.97 (s, 1H), 7.30-7.50 (m, 5H), 7.73-7.82 (m, 3H), 7.96 (s, 1H).  
IR (KBr):  $\nu$  3240 (w), 3060 (w), 1618 (m), 1595 (s), 1559 (s), 1439 (m), 1403 (s), 1380 (s), 1305 (s), 766 (w), 696 (w)  $\text{cm}^{-1}$ .

Example 5(b)

50 4-phenylmethylamino-2-(1,2,4-triazol-1-yl)quinazoline

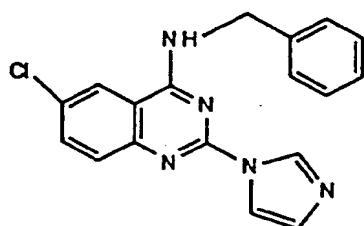
55



10 mp : 193-195 °C.  
NMR ( $\text{CDCl}_3$ ):  $\delta$  4.73 (d, 2H), 6.02 (bs, 1H), 7.1-7.74 (m, 8H), 7.59-7.65 (m, 3H).  
IR (KBr):  $\nu$  3240 (w), 3125 (w), 1618 (m), 1596 (s), 1580 (s), 1547 (s), 1491 (m), 1384 (s), 1314 (s), 1207 (s), 1052 (w), 763 (m), 698 (m)  $\text{cm}^{-1}$ .

15 Example 5(c)

4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline



25 mp : 260-264 °C (dec.).  
NMR (200MHz, DMSO-d6):  $\delta$  4.84 (d, 2H), 7.09 (s, 1H), 7.28-7.50 (m, 5H), 7.70 (d, 1H), 7.82 (dd, 1H), 7.93 (s, 1H), 8.52 (d, 1H), 8.56 (s, 1H), 9.40 (broad, 1H).

30 Example 5(d)

4-phenylmethylamino-2-((1-imidazolyl)methyl)quinazoline

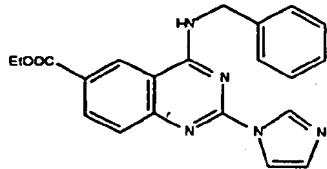


40 mp : 174 - 176 °C.  
NMR (200MHz, DMSO-d6):  $\delta$  4.70 (d, 2H), 5.18 (s, 2H), 6.88 (s, 1H), 7.16 (s, 1H), 7.17-7.40 (m, 4H), 7.50 (m, 1H), 7.60-7.82 (m, 3H), 8.28 (d, 1H), 8.92 (m, 1H).

45 Example 5(e)

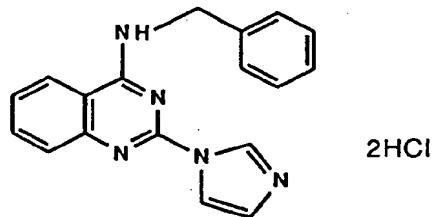
6-ethoxycarbonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline

EP 0 579 496 A1



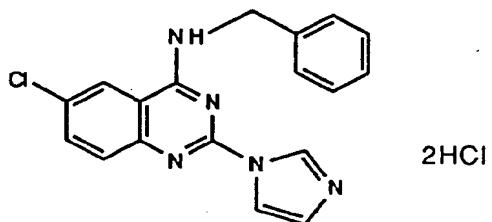
mp : 193 °C (dec.)  
 10 NMR (200MHz, CDCl<sub>3</sub>) δ: 1.58 (t, 3H), 4.69-4.80(m, 4H), 6.62 (br, 1H), 7.17 (s, 1H), 7.35-7.44 (m, 5H), 7.89 (d, 1H), 7.98 (s, 1H), 8.24 (dd, 1H), 8.58 (d, 1H), 8.67 (s, 1H).  
 IR (KBr) v: 3275, 1652, 1626, 1588, 1472, 1438, 1314, 1093, 1055, 1014 cm<sup>-1</sup>.

15 Example 6  
 15 4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride



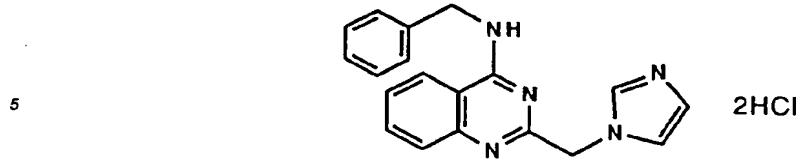
The title compound having the following physical data, was obtained by the same procedure as Example 2, by using the free base prepared in Example 5 and HCl/methanol solution.  
 30 mp : 248-250 °C.  
 NMR (200MHz, DMSO-d<sub>6</sub>): δ 4.96 (d, 2H), 7.20-7.40 (m, 3H), 7.50-7.54 (m, 2H), 7.63 (t, 1H), 7.75-7.81 (m, 1H), 7.88-7.90 (m, 2H), 8.43 (s, 1H), 8.55 (d, 1H), 9.85 (broad t, 1H), 10.03 (s, 1H).  
 IR (KBr): v 3055 (broad), 2655 (broad), 1634 (s), 1569 (s), 1520 (m), 1472 (m), 1395 (s), 760 (w) cm<sup>-1</sup>.  
 By the same procedure as described in Reference example 13 and 14 and Example 5 and 6, the below  
 35 compounds having the following physical data were given.

40 Example 6(a)  
 40 4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 186 °C (dec.).  
 NMR (200MHz, DMSO-d<sub>6</sub>): δ 4.95 (m, 2H), 7.25-7.40 (m, 3H), 7.49-7.53 (m, 2H), 7.78 (d, 1H), 7.90 (t, 1H), 7.92 (dd, 1H), 8.43 (t, 1H), 8.71 (d, 1H), 9.88 (broad, 1H), 10.03 (t, 1H).

55 Example 6(b)  
 55 4-phenylmethylamino-2-((1-imidazolyl)methyl)quinazoline dihydrochloride

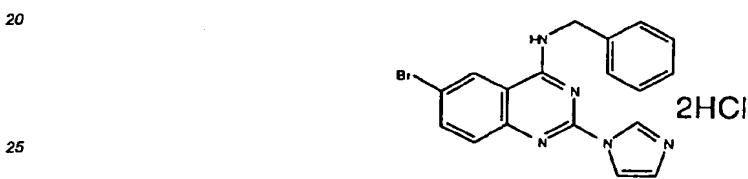


mp : 306 °C(dec.).  
10 NMR (200MHz, DMSO-d6): δ 4.64 (m, 2H), 5.81 (s, 2H), 7.17-7.40 (m, 5H), 7.68-8.10 (m, 5H), 8.68 (m, 1H), 9.26 (s, 1H).

The following compound was obtained by the same procedure as described in Reference example 13, 14 and example 5 and 6, by using the corresponding (1H,3H)-quinazoline-2,4-dione or its derivative and corresponding amine.

15 Example 6(c)

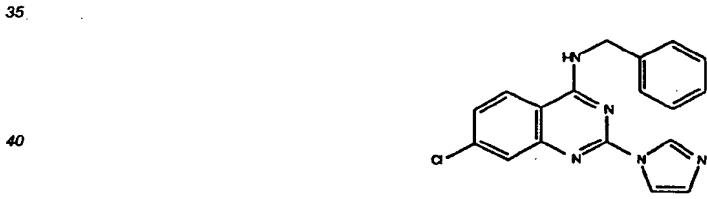
6-bromo-4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 199-202 °C, (dec.).  
NMR (200MHz, DMSO-d6) δ: 4.95 (m, 2H), 7.25-7.40 (m, 3H), 7.49-7.53 (m, 2H), 7.70 (d, 1H), 7.81 (t, 1H), 8.01 (dt, 1H), 8.38 (d, 1H), 8.81 (d, 1H), 9.80 (broad, 1H), 9.88 (d, 1H).

Example 6(d)

7-chloro-4-phenylmethylamino-2-(1-imidazolyl)quinazoline

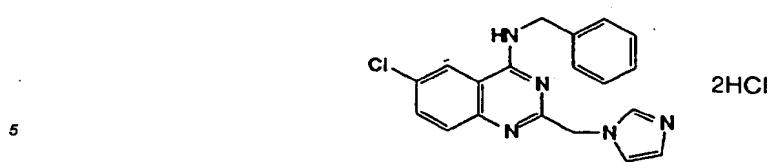


mp : 265-268 °C  
45 NMR (200MHz, DMSO-d6) δ: 4.85 (s, 2H), 7.08 (s, 1H), 7.21-7.40 (m, 3H), 7.42-7.58 (m, 2H), 7.71 (s, 1H), 7.91 (s, 1H), 8.35 (d, 1H), 8.54 (s, 1H).  
IR (KBr): ν 3260 (w), 3135 (w), 1609 (s), 1570 (s), 1473 (s), 1451 (s), 1418 (s), 1349 (m), 1307 (m), 1037 (m), 778 (w), 698 (w) cm⁻¹.

50 Example 6(e)

6-chloro-4-phenylmethylamino-2-(1-imidazolylmethyl)quinazoline dihydrochloride

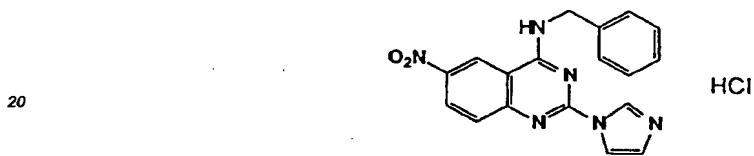
EP 0 579 496 A1



mp : 290 °C, (dec.)  
NMR (200MHz, DMSO-d6) δ: 4.66 (d, 2H), 5.72 (s, 2H), 7.18-7.42 (m, 5H), 7.72-8.05 (m, 4H), 8.76 (s, 1H), 9.27 (s, 1H).

Example 6(f)

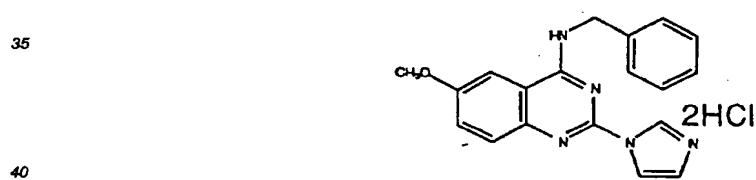
15 6-nitro-4-phenylmethylamino-2-(1-imidazolyl)quinazoline hydrochloride



mp : 190 °C, (dec.)  
25 NMR (200MHz, DMSO-d6) δ: 5.00 (m, 2H), 7.25-7.42 (m, 3H), 7.45-7.53 (m, 2H), 7.76 (broad, 1H), 7.87-7.93 (d, 1H), 8.39 (broad, 1H), 8.57-8.65 (d, 1H), 9.56 (s, 1H), 9.82 (broad, 1H), 10.28 (broad, 1H).  
IR (KBr) v: 1335(s), 1403(s), 1438(w), 1518(w), 1601(s), 3405(broad), 3445(w) cm⁻¹.

Example 6(g)

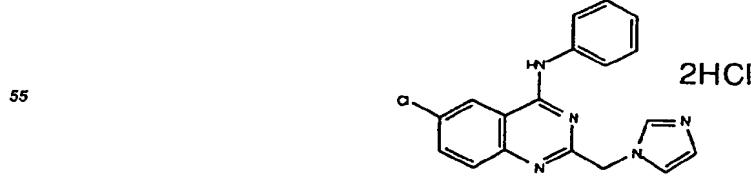
30 6-methoxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 196 °C, (dec.)  
NMR (200MHz, DMSO-d6) δ: 3.93 (s, 3H), 4.98 (m, 2H), 7.25-7.42 (m, 3H), 7.45-7.57 (m, 2H), 7.74 (d, 1H), 7.87 (d, 1H), 7.95 (d, 1H), 8.41 (d, 1H), 9.55 (broad, 1H), 9.96 (d, 1H).  
45 IR (KBr) v: 1254(m), 1395(s), 1506(m), 1558(s), 1601(s), 3065(w), 3245(w), and 3395(w) cm⁻¹.

Example 6(h)

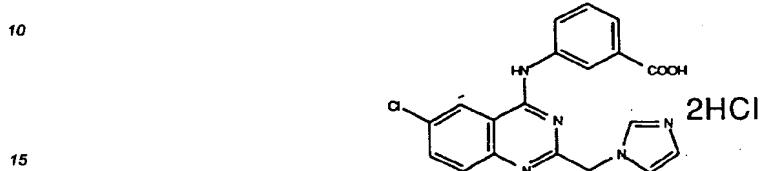
50 6-chloro-4-phenylamino-2-(1-imidazolylmethyl)quinazoline dihydrochloride



mp : 280 °C, (dec.)  
 NMR (200MHz, DMSO-d6) δ: 5.72 (s, 2H), 7.12-8.03 (m, 9H), 8.99 (m, 1H), 9.26 (s, 1H), 10.65 (bs, 1H).  
 IR (KBr) ν: 3100 (m), 2830 (m), 2565 (m), 1635 (m), 1608 (m), 1578 (sd), 1492 (ms), 1151 (m) cm⁻¹.

5    Example 6(i)

6-chloro-4-(3-carboxyphenyl)amino-2-(1-imidazolylmethyl)quinazoline dihydrochloride



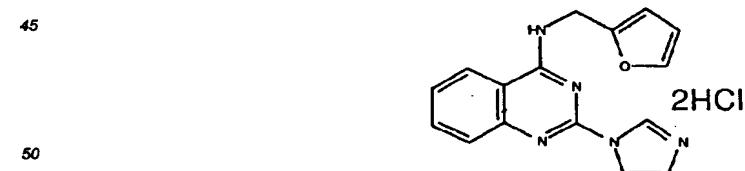
mp : 285 °C, (dec.)  
 NMR (200MHz, DMSO-d6) δ: 5.69 (s, 2H), 7.49 (t, 1H), 7.70-8.02 (m, 6H), 8.26 (m, 1H), 8.90 (m, 1H), 9.26 (s, 1H), 10.50 (bs, 1H).  
 IR (KBr) ν: 3326 (m), 3065 (m), 2835 (m), 1698 (m), 1631 (m), 1602 (m), 1561 (s), 1486 (m), 1444 (m), 1400 (m), 1376 (mw) cm⁻¹.

25    Example 6(j)  
 6-dimethylaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline hydrochloride



35    mp : 264-266°C.  
 NMR (200MHz, DMSO-d6) δ: 2.69(s, 6H), 5.00(d, 2H), 7.25-7.45(m, 3H), 7.46-7.54(m, 2H), 7.78(m, 1H), 7.93(dd, 1H), 8.13(d, 1H), 8.40(m, 1H), 8.95(m, 1H), 9.84(m, 1H), 10.13(br, 1H).  
 IR (KBr): ν 3400(m), 3320(m), 2960(w), 1597(s), 1556(m), 1520(m), 1445(m), 1398(s), 1341(s), 1164(s), 728(s), 579(s) cm⁻¹.

40    Example 6(k)  
 4-(2-furylmethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



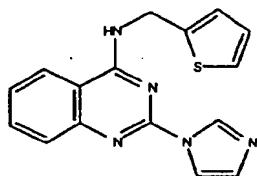
55    mp : 230 °C, (dec.)  
 NMR (200MHz, DMSO-d6) δ: 4.99 (d, 2H), 6.48 (m, 2H), 7.57-7.97 (m, 5H), 8.49 (m, 2H), 9.64 (t, 1 H), 10.08 (s, 1 H).

Example 6(l)

4-(2-thienylmethyl)amino-2-(1-imidazolyl)quinazoline

5

10



15

mp : 234-235° C  
 NMR (200MHz, DMSO-d6): δ 5.03 (d, 2H), 7.00 (m, 1H), 7.13 (s, 1H), 7.18 (d, 1H), 7.37 (d, 1H), 7.52 (t, 1H),  
 7.78 (m, 2H), 8.02 (s, 1H), 8.28 (d, 1H), 8.67 (s, 1H), 9.40 (t, 1H).

IR (KBr): v 3255 (w, broad), 1617 (w), 1668 (s), 1470 (s), 1402 (s), 1321 (m) cm<sup>-1</sup>.

20

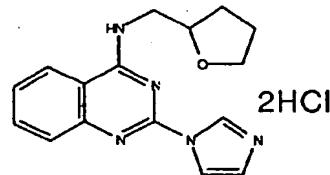
Example 6(m)

25

4-(2-tetrahydrofurylmethyl)amino-2-(1-imidazolyl)quinazoline

25

30



35

mp : 98-150 °C  
 NMR (200MHz, DMSO-d6) δ: 1.62-2.13 (m, 4H), 3.62-3.90 (m, 4H), 4.12-4.31 (m, 2H), 7.54-7.97 (m, 4H), 8.44  
 (s, 1H), 9.32 (t, 1H), 10.02 (s, 1H).  
 IR (KBr) v: 3500-2700 (s, broad), 1635 (m), 1576 (m), 1396 (m), 1063 (w), 765 (w) cm<sup>-1</sup>.

40

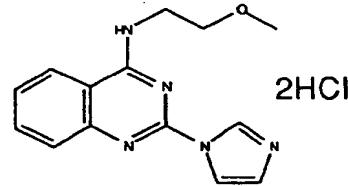
Example 6(n)

40

4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride

45

45



50

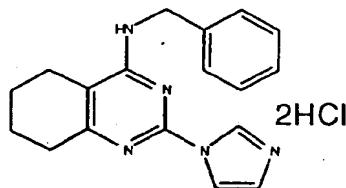
mp : 210-215 °C  
 NMR (200MHz, DMSO-d6) δ: 3.31 (s, 3H), 3.66 (t, 2H), 3.85 (q, 2H), 7.61 (t, 1H), 7.78 (d, 1H), 7.85 (m, 1H),  
 8.42 (m, 2H), 9.23 (t, 1H), 9.95 (s, 1H).

55

Example 6(o)

4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydro-quinazoline dihydrochloride

5



10 mp : 195 °C, (dec.)

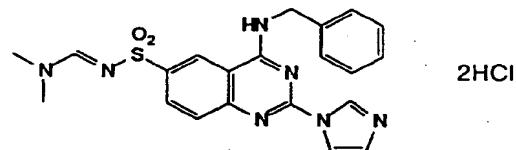
NMR (200MHz, DMSO-d6) δ: 1.79 (m, 4H), 2.45 (m, 2H), 2.66 (m, 2H), 4.74 (d, 2H), 7.17-7.48 (m, 5H), 7.83 (cs, 1H), 8.13 (t, 1H), 8.24 (cs, 1H), 9.84 (cs, 1H).

Example 6(p)

15

6-dimethylaminomethyleneamino-4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride

20



25

mp : 225 °C

NMR (200MHz, DMSO-d6) δ: 2.93 (s, 3H), 3.18 (s, 3H), 4.97 (d, 2H), 7.25-7.40 (m, 3H), 7.49-7.53 (m, 2H), 7.79 (s, 1H), 7.84 (d, 1H), 8.15 (dt, 1H), 8.30 (s, 1H), 8.39 (s, 1H), 9.00 (s, 1H), 9.86 (s, 1H), 10.10 (t, 1H).

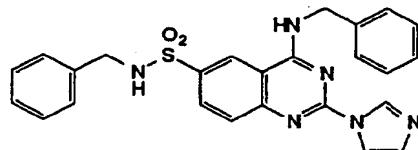
30

Example 6(q)

6-(phenylmethylamino)sulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline

35

40



mp : 207-8 °C

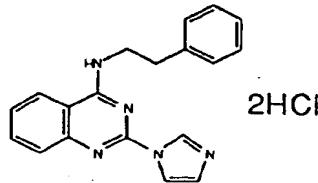
NMR (200MHz, DMSO-d6) δ: 4.09 (d, 2H), 4.89 (m, 2H), 7.11 (s, 1H), 7.16-7.52 (m, 10H), 7.79 (d, 1H), 7.96 (d, 1H), 8.07 (dd, 1H), 8.28 (t, 1H), 8.60 (s, 1H), 8.83 (m, 1H), 9.80 (broad t, 1H).

Example 6(r)

50

4-(2-phenylethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride

55



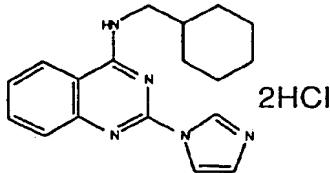
mp : 70-100 °C

NMR (200MHz, DMSO-d6) δ: 3.05 (t, 2H), 3.95 (q, 2H), 7.12-7.38 (m, 6H), 7.57 (t, 1H), 7.73 (m, 2H), 7.89 (m, 3H), 8.41 (m, 2H), 9.38 (t, 1H), 9.96 (s, 1H).

**5 Example 6(s)**

4-cyclohexylmethylamino-2-(1-imidazoly)quinazoline dihydrochloride

10



15

mp : 140-150 °C

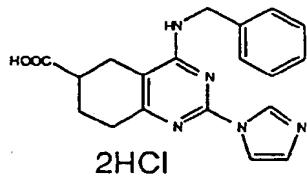
NMR (200MHz, DMSO-d6) δ: 0.98-1.32 (m, 5H), 1.53-1.90 (m, 6H), 3.58 (t, 2H), 7.59 (t, 1H), 7.77 (m, 1H), 7.89 (t, 2H), 8.41 (s, 1H), 8.56 (d, 1H), 9.28 (t, 1H), 9.97 (s, 1H).

20

**Example 6(t)**

6-carboxy-4-phenylmethylamino-2-(1-imidazoly)-5,6,7,8-tetrahydroquinazoline dihydrochloride

25



30

mp : 105 °C (dec.)

NMR (200MHz, DMSO-d6) δ: 1.82 (m, 1H), 2.10 (m, 1H), 2.71 (m, 5H), 4.74 (d, 2H), 7.18-7.47 (m, 5H), 7.82 (s, 1H), 8.24 (s, 1H), 8.25 (m, 1H), 9.84 (s, 1H).

IR (KBr) v: 3140 (bm), 2935 (bm), 1718 (mw), 1654 (m), 1617 (ms), 1522 (mw), 1394 (m) cm<sup>-1</sup>.

40

**Example 6(u)**  
6-phenylmethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazoly)quinazoline dihydrochloride

45



50

mp : 235-237 °C

NMR (200MHz, DMSO-d6) δ: 4.54 (d, 2H), 7.20-7.40 (m, 8H), 7.48-7.52 (m, 2H), 7.70 (s, 1H), 7.81 (d, 1H), 8.31 (dd, 1H), 8.37 (s, 1H), 9.09 (s, 1H), 9.22 (br, 1H), 9.82 (s, 1H), 9.89 (br, 1H).

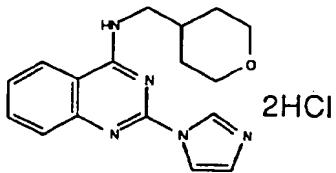
IR (KBr) v: 3500-3000 (br), 1647, 1604, 1555, 1453, 1398, 1315, 699 cm<sup>-1</sup>.

55

**Example 6(v)**

4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazoly)quinazoline dihydrochloride

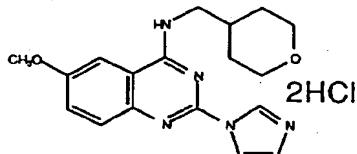
EP 0 579 496 A1



mp : 160-195 °C  
 10 NMR (200MHz, DMSO-d6) δ: 10.0 (m, 1H), 9.29 (m, 1H), 8.53 (d, 1H), 8.45 (m, 1H), 7.82-7.95 (d, 2H), 7.75 (d, 1H), 7.60 (t, 1H), 3.86 (m, 2H), 3.64 (m, 2H), 3.28 (t, 2H), 2.02 (m, 1H), 1.60-1.75 (m, 2H), 1.21-1.48 (m, 2H).  
 IR (KBr) v: 1635, 1604, 1562, 1524, 1471, 1443, 1393, 1091, 762 cm⁻¹.

15 Example 6(w)

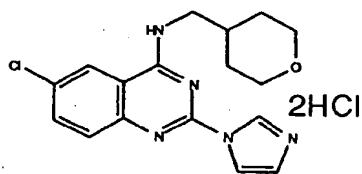
6-methoxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



25 mp : 170-190 °C  
 NMR (200MHz, DMSO-d6) δ: 9.96 (s, 1H), 9.15 (m, 1H), 9.42 (s, 1H), 7.98 (s, 1H), 7.89 (s, 1H) 7.71 (d, 1H), 7.52 (dd, 1H), 3.94 (s, 3H), 3.80-3.95 (m, 2H), 3.62 (m, 2H), 3.29 (t, 2H), 2.02 (m, 1H), 1.60-1.75 (m, 2H), 1.20-1.49 (m, 2H).  
 IR (KBr) v: 1637, 1605, 1569, 1524, 1473, 1440, 1391, 1251, 1091, 1020 cm⁻¹.

Example 6(x)

35 6-chloro-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



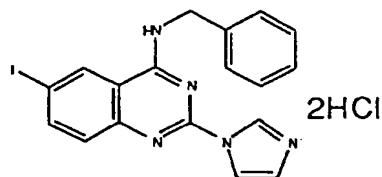
45 mp : 155-185 °C  
 NMR (200MHz, DMSO-d6) δ: 9.89 (s, 1H), 9.25 (m, 1H), 8.66 (m, 1H), 8.41 (m, 1H), 7.72-7.96 (m, 3H), 3.81-3.95 (m, 2H), 3.56-3.70 (m, 2H), 3.28 (t, 2H), 2.02 (m, 1H), 1.63-1.79 (m, 2H), 1.20-1.46 (m, 2H).  
 IR (KBr) v: 1604, 1577, 1524, 1497, 1446, 1396, 1349, 1089 cm⁻¹.

50 Example 6(y)

6-iodo-4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride

55

5



mp : 183 °C, (dec.)  
 NMR (200MHz, DMSO-d6) δ: 4.95 (m, 2H), 7.25-7.40 (m, 3H), 7.45-7.60 (m, 3H), 7.88 (t, 1H), 8.16 (dt, 1H), 8.43 (t, 1H), 8.93 (s, 1H), 9.78 (t, 1H), 10.01 (d, 1H).  
 IR (KBr) v: 3060, 2685, 1634, 1600, 1541, 1406, 1390 cm<sup>-1</sup>.

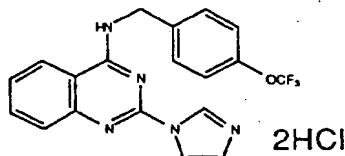
15

example 6(z)

15

4-(4-trifluoromethoxyphenoxy)methylamino-2-(1-imidazolyl)quinazoline dihydrochloride

20



25

mp : 140-145 °C  
 NMR (200MHz, DMSO-d6) δ: 5.01 (m, 2H), 7.30-7.40 (m, 2H), 7.60-7.88 (m, 6H), 8.42-8.55 (m, 2H), 9.78 (bm, 1H), 10.35 (s, 1H).  
 IR (KBr) v: 3070, 1634, 1604, 1560, 1525, 1394, 1263, 1224, 1164 cm<sup>-1</sup>.

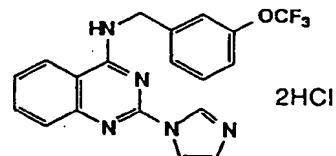
30

Example 6(aa)

35

4-(3-trifluoromethoxyphenoxy)methylamino-2-(1-imidazolyl)quinazoline dihydrochloride

40



45

(2HCl salt)  
 mp : 170-180°C  
 NMR (200MHz, DMSO-d6): δ 5.01 (d, 2H), 7.25(d, 1H), 7.42-7.71 (m, 3H), 7.81(s, 1H), 7.88(m, 2H), 8.44(s, 1H), 8.54(d, 1H), 9.95(t, 1H), 10.06(s, 1H).  
 IR(KBr): v 3430(w), 3020(w), 2960(w), 1653(s), 1603(s), 1542(m), 1396(s), 1270(s), 1216(m) cm<sup>-1</sup>

50

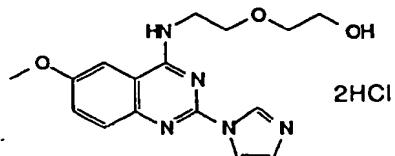
Example 6(bb)

55

6-methoxy-4-(2-(2-hydroxyethoxy)ethylamino-2-(1-imidazolyl)quinazoline dihydrochloride

EP 0 579 496 A1

5



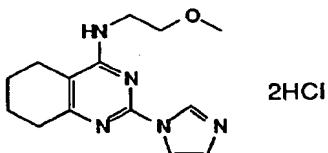
(2HCl salt)  
mp : 167.5-170°C

NMR (200MHz, DMSO-d6): δ 3.51 (s, 4H), 3.75-3.78(m, 2H), 3.85-3.90(m, 2H), 3.93(s, 3H), 7.49(dd, 1H), 7.70(d, 1H), 7.84(t, 1H), 7.98(m, 1H), 8.39(m, 1H), 9.19(br, 1H), 9.90(t, 1H).  
IR(KBr): ν 3270(s), 2940(m), 1610(s), 1557(m), 1513(s), 1396(s), 1247(m), 1115(m), 1029(w) cm -1

15 Example 6(cc)

4-(2-methoxyethylamino)-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline dihydrochloride

20



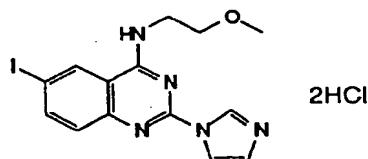
25

(2HCl salt)  
mp : 140-142.5°C  
NMR (200MHz, DMSO-d6): δ 1.77(s, 4H), 2.38(s, 2H), 2.65(s, 2H), 3.28(s, 3H), 3.54(t, 3H), 3.57(d, 2H), 7.49(br, 1H), 7.84(s, 1H), 8.30(s, 1H), 9.86(s, 1H).  
IR(KBr): ν 3230-2355(br, m), 1555(s), 1506(s), 1526(s), 1449(w), 1395(s), 1101(m), 828(w), 756(m) cm -1

Example 6(dd)

35 4-(2-methoxyethylamino)-6-iodo-2-(1-imidazolyl)quinazoline dihydrochloride

40



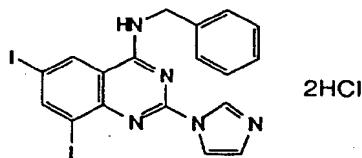
45 (2HCl salt)

mp : 159-161°C  
NMR (200MHz, DMSO-d6): δ 3.31 (s, 3H), 3.67(t, 2H), 3.88(t, 2H), 7.54(d, 1H), 7.85(t, 1H), 8.13(dd, 1H), 8.42(t, 1H), 8.89(d, 1H), 9.20(t, 1H), 9.94(t, 1H).  
IR(KBr): ν 3205-2365(m, br), 1633(s), 1604(s 1564(s), 1541(s), 1506(s), 1459(m), 1409(s), 1367(s), 1193(w), 1114(m), 1011(m), 859(w), 833(m), 777(m), 713(w), 621(w), 526(w) cm -1

55 Example 6(ee)

4-phenylmethylamino-6,8-diiodo-2-(1-imidazolyl)quinazoline dihydrochloride

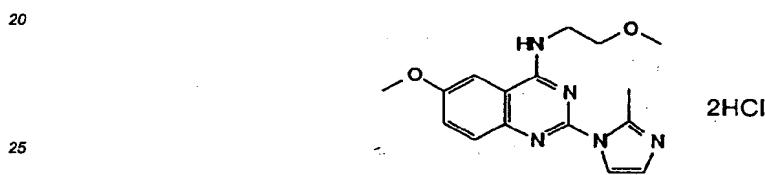
EP 0 579 496 A1



(2HCl salt)  
10 mp : 303-304°C (dec.)  
NMR (200MHz, DMSO-d6): δ 4.94(d, 2H), 7.33(dd, 3H), 7.49(dd, 2H), 7.74(t, 1H), 8.24(t, 1H), 8.67(t, 1H), 8.88(d, 1H), 9.66(s, 1H), 9.77(br, 1H).  
IR(KBr): ν 3410-2365(br, m), 1599(s), 1437(m), 1387(s), 1350(m), 1314(m), 1273(w), 1061(w), 1020(w), 793(w), 748(w), 701(w), 620(w) cm -1

15 Example 6(ff)

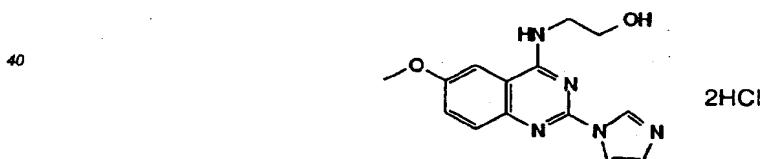
4-(2-methoxyethyl)amino-6-methoxy-2-(2-methyl-1-imidazolyl)quinazoline dihydrochloride



(2HCl salt)  
mp : 263-264°C  
30 NMR (200MHz, DMSO-d6): δ 3.04(s 3H), 3.31 (s 3H), 3.68(m, 2H), 3.84(m, 2H), 3.92(s, 3H), 7.50(dd, 2H), 7.72(m, 2H), 7.91(s, 1H), 8.30(s, 1H), 9.10(m, 1H).  
IR(KBr): ν 3230(w), 2680(w), 1615(s), 1592(s), 1560(s), 1420(m), 1382(m), 1248(m), 909(w) cm -1

Example 6(gg)

4-(2-hydroxyethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline dihydrochloride



(2HCl salt)  
mp : 228-233°C  
NMR (200MHz, D2O): δ 3.63(t, 2H), 3.74(s, 3H), 3.83(t, 2H), 6.90(d, 1H), 7.16(dd, 1H), 7.26(d, 1H), 7.57(d, 1H), 7.96(d, 1H), 9.23(s, 1H).  
50 IR(KBr): ν 2700-3400(br), 1605(s), 1569(m), 1520(m), 1394(m), 1246(w), 1040(w), 815(w) cm -1

Example 6(hh)

4-(2-methoxyethyl)amino-6,8-diiodo-2-(1-imidazolyl)quinazoline dihydrochloride

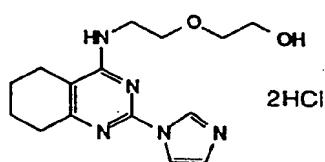
55

EP 0 579 496 A1



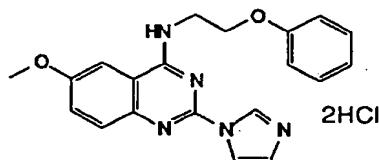
(2HCl salt)  
 10 mp : 244-246.5°C  
 NMR (200MHz, DMSO-d6): δ 3.31(3H), 3.65(2H), 3.89(2H), 7.79(s, 1H), 8.29(s, 1H), 8.68(s, 1H), 8.89(s, 1H), 9.32(br, 1H).  
 IR(KBr): ν 3240-2335(br, m), 1598(s), 1553(w), 1523(w), 1476(m), 1436(m), 1383(m), 1354(m), 1275(w), 1107(w), 1086(m), 1018(m), 991(w), 860(w), 793(m), 752(w), 724(w), 615(w) cm⁻¹

15 Example 6(ii)  
 4-(2-(2-hydroxyethoxyethyl)amino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline dihydrochloride



25 (2HCl salt)  
 mp : 125-128°C  
 30 NMR (200MHz, DMSO-d6): δ 1.80(4H), 2.40(2H), 3.65(br, 8H), 7.45(br, 1H), 7.85(d, 1H), 8.30(d, 1H), 9.85(d, 1H).  
 IR(KBr): ν 3380(s), 3120(s), 2945(m), 2755-2460(m), 1615(s), 1540(s), 1457(m), 1428(m), 1390(s), 1350(m), 1319(w), 1103(m), 1070(m), 829(w), 624(w) cm⁻¹

35 Example 6(ji)  
 4-(2-phenoxyethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline and its dihydrochloride



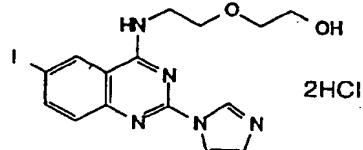
45 (free base)  
 mp : 213-214°C  
 NMR (200MHz, DMSO-d6): δ 3.89 (s, 3H), 4.04(d, 2H), 4.31 (t, 2H), 6.93-7.01(3H), 7.08(d, 1H), 7.28(td, 2H), 7.45(dd, 1H), 7.64(d, 1H), 7.78(d, 1H), 7.93(t, 1H), 8.57(s, 1H), 9.85(br, 1H).  
 IR(KBr): ν 1599(s), 1555(s), 1491(s), 1409(s), 1382(w), 1310(m), 1242(s), 1051(s), 752(w) cm⁻¹  
 (2HCl salt)  
 mp : 184-186°C  
 NMR (200MHz, DMSO-d6): δ 3.94(s, 3H), 4.12(d, 2H), 4.33(t, 2H), 6.90-7.01(3H), 7.29(t, 2H), 7.53(dd, 1H), 7.88(t, 1H), 7.96(d, 1H), 8.40(t, 1H), 9.31(br, 1H), 9.93(d, 1H).  
 IR(KBr): ν 3050(m), 2840-2335(m), 1637(s), 1598(s), 1497(m), 1472(m), 1380(s), 1258(s), 1122(w), 1077(w), 1029(m), 775(m), 747(m) cm⁻¹

Example 6(kk)

4-(2-(2-hydroxyethoxy)ethyl)amino-6-iodo-2-(1-imidazolyl)quinazoline and its dihydrochloride

5

10



(free base)

NMR (200MHz, DMSO-d6):  $\delta$  3.50(s, 4H), 3.75(dd, 2H), 3.78(d, 2H), 4.59(br, 1H), 7.10(d, 1H), 7.47(dd, 1H), 7.95(d, 1H), 8.05(d, 1H), 8.52(d, 1H), 8.75(s, 1H), 8.57(br, 1H).

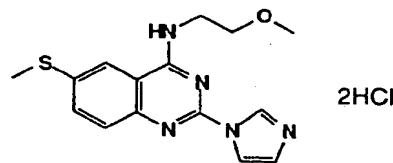
(2HCl salt)

mp : 132-135°C

NMR (200MHz, DMSO-d6):  $\delta$  3.50(s, 4H), 3.75(d, 2H), 3.86(d, 2H), 7.53(d, 1H), 7.83(s, 1H), 8.15(dd, 1H), 8.40(s, 1H), 8.89(d, 1H), 9.22(br, 1H), 9.90(s, 1H).IR(KBr):  $\nu$  3230-2720(br, m), 1607(s), 1555(m), 1526(m), 1492(m), 1445(m), 1394(s), 1348(m), 1118(m), 1063(m), 1027(m), 859(m), 622 cm<sup>-1</sup>Example 6(lI)

25 4-(2-methoxyethyl)amino-6-methylthio-2-(1-imidazolyl)quinazoline and its dihydrochloride

30



(free base)

mp : 201-202°C

NMR (200MHz, DMSO-d6):  $\delta$  2.61 (s, 3H), 3.32(s, 3H), 3.65(m, 2H), 3.81(m, 2H), 7.10(s, 1H), 7.58-7.73(m, 2H), 7.95(s, 1H), 8.10(s, 1H), 8.59(s, 1H), 8.83(t, 1H).

(2HCl salt)

40 mp : 230-232°C

NMR (200MHz, DMSO-d6):  $\delta$  2.65(s, 3H), 3.31(s, 3H), 3.66(m, 2H), 3.88(m, 2H), 7.64-7.83(m, 2H), 7.89(s, 1H), 8.24(m, 1H), 8.42(s, 1H), 9.28(t, 1H), 9.98(s, 1H).Example 6(mm)

45

4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylthio-2-(1-imidazolyl)quinazoline

50



55

(free base)

mp : 169-172 °C

NMR (200MHz, DMSO-d6):  $\delta$  2.61 (s 3H), 3.51 (s 4H), 3.76(m, 4H), 4.60(m, 1H), 7.10(s, 1H), 7.57-7.76(m,

2H), 7.95(s, 1H), 8.09(s, 1H), 8.59(s, 1H), 8.82(m, 1H).

Example 6(nn)

5 4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylthio-2-(1-imidazolyl)quinazoline dihydrochloride

10



15 (2HCl salt)

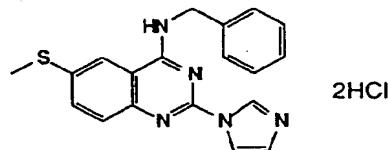
mp : 180-182 °C.

NMR (200MHz, DMSO-d6): δ 2.65(s, 3H), 3.51 (s, 4H), 3.75(m, 2H), 3.90(m, 2H), 7.64-7.82(m, 2H), 7.87(m, 1H), 8.26(m, 1H), 8.42(1H), 9.34(t, 1H), 9.98(m, 1H).

20 Example 6(o0)

6-methylthio-4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride

25



30

mp : 192-195 °C.

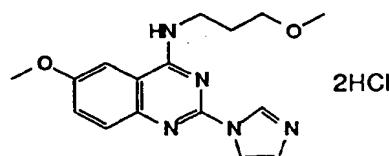
NMR (200MHz, DMSO-d6): δ 2.64(s, 3H), 4.96(d, 2H), 7.31-7.86(m, 9H), 8.26(s, 1H), 8.40(s, 1H), 9.75(t, 1H), 9.96(s, 1H).

35 IR (KBr): ν 3210(w), 3040(m), 2600(m), 1630(s), 1556(s), 1495(m), 1433(m), 1510(s), 1339(m), 1203(w), 1112(w), 1091(w), 1013(w), 823(w), 743(m), 704(n), 615(w) cm⁻¹.

Example 6(pp)

40 4-(3-methoxypropyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline dihydrochloride

45



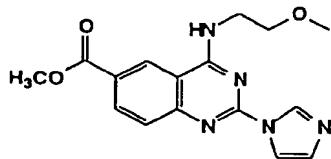
50 mp : 191-194°C.

NMR (200MHz, DMSO-d6): δ 1.94(m, 2H), 3.25(s, 3H), 3.42(t, 2H), 3.69(m, 2H), 3.90(s, 3H), 7.45(m, 1H), 7.64(d, 1H), 7.86(m, 1H), 7.99(m, 1H), 8.35(m, 1H), 9.30(m, 1H), 9.88(m, 1H).

IR (KBr): ν 1641, 1603, 1587, 1573, 1529, 1421, 1382, 1253, 1111, 1027, 858 cm⁻¹.

55 Example 6(qq)

4-(2-methoxyethyl)amino-6-methoxycarbonyl-2-(1-imidazolyl)quinazoline



mp : 252-253°C.

10 NMR (200MHz, DMSO-d6): δ 3.32(s, 3H), 3.66(t, 2H), 3.83(t, 2H), 3.92(s, 3H), 7.13(s, 1H), 7.75(d, 1H), 7.98(s, 1H), 8.23(s, 1H), 8.63(s, 1H), 9.02(s, 1H), 9.28.  
IR (KBr) : ν 3245(w), 3140(w), 2900(w), 1724(s), 1601(s), 1473(s), 1437(s), 1407(s), 1310(s), 1119(m), 1021(m), 766 cm<sup>-1</sup>.

15 Example 6(rr)

4-[2-(2-hydroxyethoxy)ethyl]amino-6-methoxycarbonyl-2-(1-imidazolyl)-quinazoline



mp : 233-235°C.

NMR (200MHz, DMSO-d6): δ 3.50(m, 4H), 3.70-3.90(m, 4H), 3.93(s, 3H), 4.60(m, 1H), 7.12(s, 1H), 7.75(d, 1H), 7.99(s, 1H), 8.25(dd, 1H), 8.63(s, 1H), 9.03(m, 1H), 9.28(m, 1H).  
30 IR (KBr) : ν 3245(mw), 2950(w), 1730(ms), 1626(w), 1603(s), 1558(m), 1474(m), 1437(m), 1406(m), 1309(m), 1281(w), 1229(w), 1125(w), 1102(w), 1051(w) cm<sup>-1</sup>.

Example 6(ss)

35 4-(2-methylthioethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline



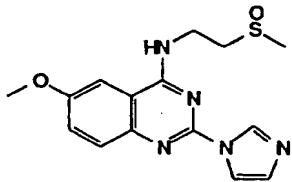
45 mp : 168-178°C.

NMR (200MHz, DMSO-d6): δ 2.17(s, 3H), 2.89(t, 2H), 3.90(m, 2H), 3.93(s, 3H), 7.55(dd, 1 H), 7.69(d, 1H), 7.87(s, 1H), 7.97(s, 1H), 8.40(s, 1H), 9.34(t, 1H), 9.93(s, 1H).  
IR (KBr) : ν 3410, 3095, 2675, 1635, 1609, 1587, 1400, 1264, 1018 cm<sup>-1</sup>.

50 Example 6(tt)

4-(2-methylsulfinylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline

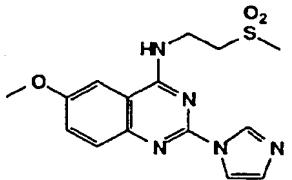
55



10 mp : 238-242°C.  
 NMR (200MHz, DMSO-d6): δ 2.63(s, 3H), 3.10-3.70(m, 4H), 3.92(s, 3H), 7.53(dd, 1H), 7.72(d, 1H), 7.88(d, 2H),  
 8.48(s, 1H), 9.43(m, 1H), 10.01(s, 1H).  
 IR (KBr) : n 3435, 3005, 2710, 1625, 1560, 1398, 1248, 1020, 825 cm<sup>-1</sup>.

15 Example 6(uu)

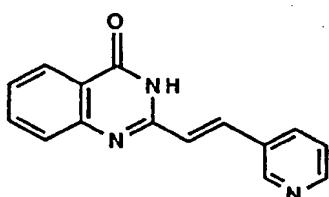
4-(2-methylsulfonylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline



25 mp : 245-252°C.  
 NMR (200MHz, DMSO-d6): δ 3.09(s, 3H), 3.61 (t, 2H), 3.92(s, 3H), 4.09(m, 2H), 7.54(dd, 1H), 7.76(d, 1H),  
 7.88(s, 2H), 8.45(s, 1H), 9.38(br, 1H), 9.89(s, 1H).

30 Reference example 15

2-(2-(3-pyridyl)vinyl)quinazolin-4-one



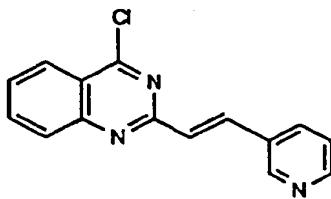
40 A mixture of 2-methylquinazolin-4-one (6.1 g) and 3-pyridinecarbaldehyde (4.1 g) in acetic acid (80 mL)  
 was heated to reflux for 20 hours. After cooling to room temperature, the precipitate was collected by filtration,  
 washed with methanol and dried to obtain the title compound as an acetic acid salt (10.5 g).

45 Reference example 16

50 4-chloro-2-(2-(3-pyridyl)vinyl)quinazoline

55

5

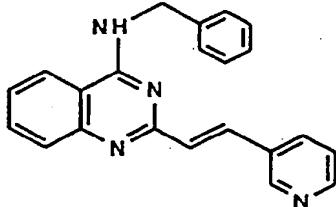


10 A suspension of the quinazolinone compound (2.9 g, prepared in Reference example 15) in thionyl chloride (25 mL) and a few drops of dimethylformamide was heated at reflux for three hours. The mixture was then concentrated, the concentrate poured into 150 mL portions of chloroform, dried over potassium carbonate and concentrated to obtain the title compound (1.1 g) as a red oil.

15 Example 7

4-phenylmethylamino-2-(2-(3-pyridyl)vinyl)quinazoline

20



25

30 The title compound having the following physical data, was obtained by the same procedure as Example 1, by using the 4-chloro compound prepared in Reference example 16 and phenylmethylamine. The product was purified by column chromatography.

mp : 178-179°C.

NMR ( $\text{CDCl}_3$ ):  $\delta$  4.96 (d, 2H), 6.11 (broad, 1H), 7.30-7.55 (m, 8H), 7.70-7.81 (m, 2H), 7.99 (d, 1H), 8.34 (s, 1H), 8.36-8.45 (m, 1H), 8.55-8.58 (dd, 1H), 8.90-8.91 (d, 1H).

35 IR (KBr):  $\nu$  3300 (m), 1577 (s), 1528 (s), 1434 (m), 1378 (s), 763 (m), 699 (m)  $\text{cm}^{-1}$ .

Example 8

40 6-ethoxycarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline and its salt

40



45

To 349 mg (1.0 mmol) of a compound prepared in example 6(t) dissolved in 20 mL of tetrahydrofuran was added 0.4 mL of thionyl chloride. Initially, a white precipitate formed, but gradually all dissolved. After stirring for 15 minutes, 20 mL of ethanol was added. After stirring an additional 15 minutes, the mixture was concentrated, the concentrate triturated in ether and collected. The solid was found to be very hygroscopic, was taken up in chloroform, treated with potassium carbonate solution, separated, dried over anhydrous magnesium sulfate and concentrated. Obtained 278 mg (0.7 mmol, 73% yield) of the desired product as a white solid (free base).

(free base)

mp : 196-198°C

NMR ( $\text{DMSO-d}_6$ ):  $\delta$  1.30 (t, 3H), 1.90 (m, 1H), 2.28 (m, 1H), 2.60 (m, 2H), 2.82 (m, 3H), 4.23 (q, 2H), 4.77 (d,

2H), 5.12 (m, 1H), 7.10 (s, 1H), 7.37 (m, 5H), 7.83 (s, 1H), 8.54 (s, 1H).

IR (KBr): 3245 (w), 1725 (ms), 1605 (s), 1532 (w), 1473 (m), 1426 (m), 1333 (w) cm<sup>-1</sup>.

To a suspension of 240 mg (0.64 mmol) of the compound prepared above in 5 mL of ethanol was added 2 mL of ~10% HCl in methanol. All the material gradually dissolved. After ten minutes, the mixture was concentrated in vacuo, triturated in ether and filtered to obtain 229 mg (0.51 mmol) of the desired product.

(2HCl salt)

mp : 158-161 °C

NMR (200MHz, DMSO-d6) δ: 1.22 (t, 3H), 1.87 (m, 1H), 2.14 (m, 1H), 2.55-3.00 (m, 5H), 7.79 (s, 1H), 8.23 (s, 1H), 9.77 (s, 1H).

IR (KBr) v: 3225, 1718, 1642, 1612, 1518, 1393 cm<sup>-1</sup>.

#### Example 8(a)

6-ethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazoly)-5,6,7,8-tetrahydroquinazoline dihydrochloride

15



25 By the same procedure as described in example 8, by using ethylamine instead of ethanol, the title compound having the following physical data was given.

mp : 147 °C, (dec.)

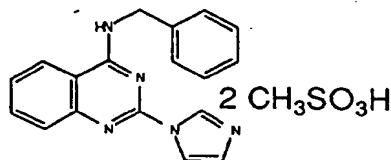
NMR (200MHz, DMSO-d6) δ: 1.04 (q, 3H), 1.65-2.06 (m, 2H), 2.50-2.80 (m, 5H), 3.10 (m, 2H), 4.72 (m, 2H), 7.18-7.48 (m, 5H), 7.81 (s, 1H), 8.05 (t, 1H), 8.18 (M, 1H), 8.24 (m, 1H), 9.82 (s, 1H).

30 IR (KBr) v: 3265-2580, 2365, 1653, 1613, 1576, 1540, 1449, 1390, 1352, 1144, 1060, 750, 701, 624 cm<sup>-1</sup>.

#### Example 9

4-phenylmethylamino-2-(1-imidazoly)quinazoline dimethanesulfonate

35



45 By the same procedure as described in Reference example 13 and 14 and example 5 and 6, by using methanesulfonic acid instead of hydrochloric acid, the title compound and the following compounds having the following physical data were given.

mp : 140-143 °C

NMR (200MHz, DMSO-d6) δ: 2.38 (s, 6H), 4.95 (m, 2H), 7.20-8.00 (m, 9H), 8.40-8.53 (m, 2H), 9.64 (t, 1H), 10.00 (s, 1H).

50

#### Example 9(a)

6,7-dimethoxy-4-phenylmethylamino-2-(1-imidazoly)quinazoline dimethanesulfonate

55



10 mp : 205 °C, (dec.)  
 NMR (200MHz, DMSO-d6) δ: 2.36 (s, 6H), 3.92 (s, 3H), 3.95 (s, 3H), 4.95 (m, 2H), 7.18 (d, 1H), 7.21-7.53 (m, 5H), 7.82 (s, 1H), 7.87 (m, 1H), 8.39 (m, 1H), 9.21 (t, 1H), 9.94 (m, 1H).

Example 9(b)

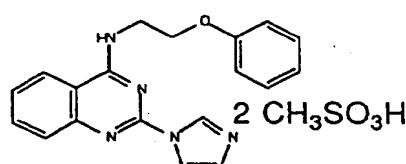
15 4-(3,4-dimethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline 1.5 methanesulfonate



mp : 163-173 °C.  
 NMR (200MHz, DMSO-d6) δ: 2.34 (s, 4H), 3.73 (d, 6H), 4.88 (d, 2H), 6.02 (d, 1H), 7.03 (d, 1H), 7.16 (s, 1H), 7.62 (t, 1H), 7.78 (d, 1H), 7.89 (m, 2H), 8.45 (d, 1H), 8.48 (s, 1H), 9.55 (t, 1H), 10.02 (s, 1H).

Example 9(c)

35 4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline dimethanesulfonate

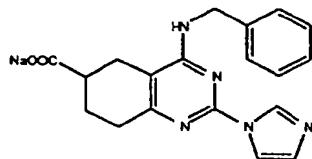


mp : 144-161 °C  
 45 NMR (200MHz, DMSO-d6) δ: 2.39 (s, 6H), 4.12 (q, 2H), 4.34 (t, 2H), 6.97 (m, 3H), 7.28 (t, 2H), 7.63 (m, 1H), 7.80 (s, 1H), 7.91 (m, 2H), 8.45 (m, 2H), 9.30 (m, 2H), 9.97 (s, 1H).  
 IR (KBr) ν: 3700-2800 (broad), 1636 (s), 1211 (s) cm<sup>-1</sup>.

Example 10

50 6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline sodium salt

55



10 A solution of 200 mg (0.57 mmol) of a compound prepared in example 6(t) dissolved in 25 mL of tetrahydrofuran was filtered to remove dark insoluble material present. To the filtrate was added 0.25 mL (0.62 mmol) of 2.5 N sodium hydroxide solution. Some precipitate formed. The mixture was concentrated and pumped in vacuum. The concentrate was triturated in tetrahydrofuran and ether and filtered. The solid was washed with ether and filtered to obtain 190 mg (0.51 mmol) of the desired product as a white solid.

15 mp : 240 °C, (dec.)

NMR (200MHz, DMSO-d<sub>6</sub>) δ: 1.50-1.82 (m, 2H), 1.88-2.35 (m, 2H), 2.59 (m, 3H), 4.62 (s, 2H), 6.98 (s, 1H), 7.12-7.48 (m, 5H), 7.73 (s, 1H), 7.86 (m, 1H), 8.33 (s, 1H).

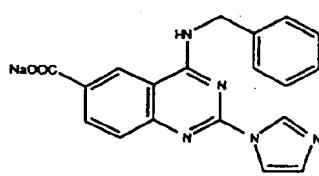
By the same procedure as described in example 10, the compound having the following physical data was given.

20

Example 10(a)

6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline sodium salt

25



30

mp : >280 °C

NMR (200MHz, DMSO-d<sub>6</sub>) δ: 4.48 (d, 2H), 6.99 (s, 1H), 7.25 (m, 1H), 7.33 (m, 4H), 7.40 (d, 1H), 7.78 (s, 1H), 7.97 (dd, 1H), 8.46 (s, 1H), 8.57 (d, 1H), 9.11 (br, 1H).

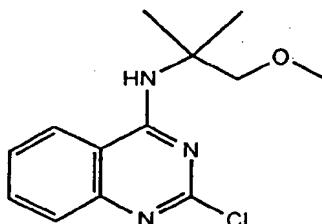
IR (KBr) v: 3500-3100 (br), 1620, 1559, 1472, 1399, 1307, 1224, 1056, 699 cm<sup>-1</sup>.

Reference example 17

40

4-(1,1-dimethyl-2-methoxyethyl)amino-2-chloroquinazoline

45



50

A mixture of 2,4-dichloroquinazoline (995 mg, 5 mmol), triethylamine (0.7 ml, 5 mmol) and 1,1-dimethyl-2-methoxyethylamine (30 mL, 0.5 M methanol sol., 15 mmol) was stood at room temperature for 1 week. The reaction mixture was concentrated and partitioned between ethyl acetate and water. Organic layer was washed with water and brine, dried over MgSO<sub>4</sub> and concentrated. The residue was purified on 50 g of silica gel column eluting with 50% ethyl acetate in hexane to obtain the title compound (176 mg) as a white solid.

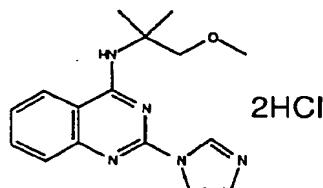
NMR (CDCl<sub>3</sub>): δ 1.60 (s, 6H), 3.46 (s, 3H), 3.56 (s, 2H), 7.38-7.80 (m, 4H).

Example 11

4-(1,1-dimethyl-2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride

5

10



15 A mixture of the compound prepared in Reference example 17 (165 mg, 0.62 mmol), imidazole (169 mg, 2.48 mmol) and phenol (0.7 g) was heated at 150 °C for 40 min. After cooling, the reaction mixture was diluted with ethyl acetate, and washed with 1N KOH and brine, and dried over MgSO<sub>4</sub>. The filtrate was concentrated to leave a viscous oil, which was purified on 8 g of silica gel column eluting with 50% ethyl acetate in hexane to obtain the title compound (165 mg, 90% yield) as a colorless amorphous.

20 (free base)  
NMR (CDCl<sub>3</sub>): δ 1.65 (s, 6H), 3.48 (s, 3H), 3.58 (s, 2H), 6.32 (broad, 1H), 7.17 (s, 1H), 7.40 (m, 1H), 7.62-7.81 (m, 3H), 7.97 (s, 1H), 8.67 (s, 1H).

To a solution of the compound above (160 mg, 0.54 mmol) in methanol (2mL) was added excess HCl-methanol solution (2mL). After stirring for 20 min at room temperature, the reaction mixture was concentrated.  
25 Excess HCl was evaporated with methanol (x3) to leave a white solid. Trituration with ether gave HCl salt (185 mg) as a white powder.

(HCl salt)  
mp : 223-225 °C  
NMR (200MHz, DMSO-d6) δ: 9.80 (s, 1H), 8.59 (m, 1H), 8.34 (m, 1H), 7.84-7.96 (m, 3H), 7.78 (m, 1H), 7.60 (m, 1H), 3.78 (s, 2H), 3.29 (s, 3H), 1.57 (s, 6H).  
30 IR (KBr) v: 1633, 1610, 1562, 1520, 1474, 1397, 1108, 754 cm<sup>-1</sup>.

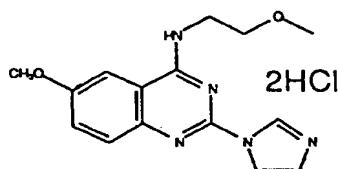
By the same procedure as described in Reference example 17 and example 11, by using corresponding amine, the compounds having the following physical data were given.

Example 11 (a)

6-methoxy-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride

40

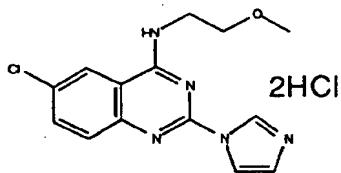
45



(HCl salt)  
mp : 169 °C, (dec.)  
NMR (200MHz, DMSO-d6) δ: 3.31, (s, 3H), 3.69 (t, 2H), 3.92 (s, 3H), 7.50 (dd, 1H), 7.88 (s, 1H), 7.97 (s, 1H), 8.42 (s, 1H), 9.21 (t, 1H), 9.99 (s, 1H).  
50 IR (KBr) v: 3380, 3200-2700, 1636, 1608, 1569, 1385, 1264, 1111, 1018 cm<sup>-1</sup>.

Example 11 (b)

55 6-chloro-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



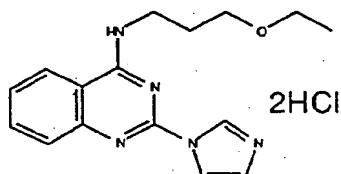
mp : 200 - 206 °C, (browning)

10 NMR (200MHz, DMSO-d6) δ: 10.0 (s, 1H), 9.32 (m, 1H), 8.68 (s, 1H), 8.43 (s, 1H), 7.85-7.96 (m, 2H), 7.77 (d, 1H), 3.90 (m, 2H), 3.66 (m, 2H), 3.32 (s, 3H).

IR (KBr) v: 1606, 1578, 1555, 1524, 1498, 1445, 1395, 1354, 1320, 1108, 1012, 876, 829 cm<sup>-1</sup>.

Example 11(c)

15 4-(3-ethoxypropyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



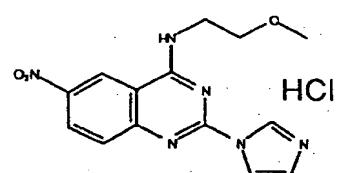
mp : 170-180 °C

NMR (200MHz, DMSO-d6) δ: 1.11 (t, 3H), 1.9 (qt, 2H), 3.38-3.54 (m, 4H), 3.74 (m, 2H), 7.60 (t, 1H), 7.78 (d, 1H), 7.90 (m, 2H), 8.44 (m, 2H), 9.22 (t, 1H), 9.97 (s, 1H).

30 IR (KBr) v: 2870-3950, 1624, 1556, 1473, 1400, 1311, 1090 cm<sup>-1</sup>.

Example 11(d)

35 6-nitro-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline hydrochloride



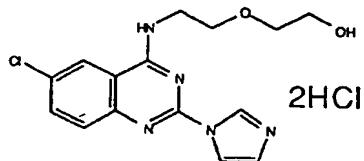
45 mp : 211 °C, (dec.)

NMR (200MHz, DMSO-d6) δ: 3.33 (s, 3H), 3.66-3.71 (m, 2H), 3.90-3.95 (m, 2H), 7.84 (m, 1H), 7.88 (d, 1H), 8.44 (m, 1H), 8.59 (m, 1H), 9.54 (m, 1H), 9.85 (bt, 1H), 9.94 (d, 1H).

IR (KBr) v: 3430, 3220-2585, 1606, 1579, 1523, 1499, 1444, 1404, 1336, 1259, 1147, 1115, 1091, 1059, 1016, 847, 825 cm<sup>-1</sup>.

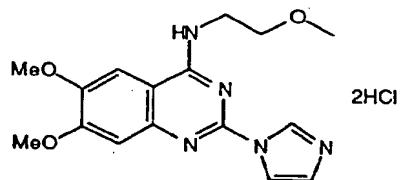
50 Example 11 (e)

55 6-chloro-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



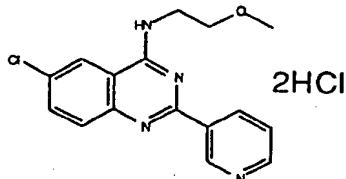
mp : 184-186 °C  
 10 NMR (200MHz, DMSO-d<sub>6</sub>) δ: 3.51 (s, 4H), 3.75-3.77 (m, 2H), 3.85-3.90 (m, 2H), 7.76 (d, 1H), 7.84 (m, 1H), 7.91 (dd, 1H), 8.40 (t, 1H), 8.67 (m, 1H), 9.30 (bt, 1H), 9.92 (m, 1H).  
 IR (KBr) v: 3320, 3175-2825, 1602, 1574, 1497, 1439, 1398, 1343, 1118 cm<sup>-1</sup>.

15 Example 11 (f)  
 16 6,7-dimethoxy-4-(2-methoxyethylamino)-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 249-251 °C  
 26 NMR (200MHz, DMSO-d<sub>6</sub>) δ: 3.32 (s, 3H), 3.65 (t, 2H), 3.85 (m, 2H), 3.94 (s, 6H), 7.16 (s, 1H), 7.88 (s, 2H), 8.39 (s, 1H), 8.92 (t, 1H), 9.95 (s, 1H).  
 30 IR (KBr) v: 3425-2365, 1642, 1603, 1573, 1511, 1481, 1456, 1386, 1287, 1240, 1156, 1132, 1109, 1021, 988, 876, 770 cm<sup>-1</sup>.

35 Example 12  
 36 6-chloro-4-(2-ethoxyethylamino)-2-(3-pyridyl)quinazoline and its salt



50 A solution of 2-(3-pyridyl)-4,6-dichloroquinazoline (1.0 g, 3.2 mmol, prepared in Reference example 5(b)) and 2-methoxyethylamine (0.53 g, 7.0 mmol) in 50 mL of ethanol was heated to reflux overnight. The solution was concentrated, taken up in chloroform and water. After some mixing, the water layer was found to be slightly acidic and was basified with sodium carbonate. The mixture was then agitated and separated. The organic layer was dried over potassium carbonate and concentrated. The concentrate was purified on silica gel column with 5% methanol in chloroform as eluent. The product obtained was combined with additional material filtered from the aqueous layer. Obtained a total of 0.35 g (1.1 mmol) of the title compound.  
 (free base)

55 mp : 210-212°C  
 56 NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.32 (s, 3H), 3.67 (t, 2H), 3.87 (qd, 2H), 7.53 (m, 1H), 7.82 (s, 2H), 8.48 (s, 1H), 8.71 (m, 3H), 9.59 (s, 1H)  
 IR (KBr): v 3250 (m), 1692 (s), 1535 (s), 1430 (w), 1412 (w), 1366 (m), 1140 (m), 823 (m) cm<sup>-1</sup>.

To a mixture of 0.35 g (1.1 mmol) of the compound prepared above in 5 mL of methanol was added 0.5 mL of 10% HCl in methanol. The solution was concentrated to 1 mL, triturated in ether, filtered and dried under vacuum. Obtained 0.33 g (0.85 mmol) of the hydrochloride.

(HCl salt)

mp : 190 °C, (dec.)

NMR (200MHz, DMSO-d<sub>6</sub>) δ: 3.32 (s, 3H), 3.71 (t, 2H), 3.94 (m, 2H), 8.01 (m, 2H), 8.12 (d, 1H), 8.75 (m, 1H), 9.01 (d, 1H), 9.20 (d, 1H), 9.66 (s, 1H).

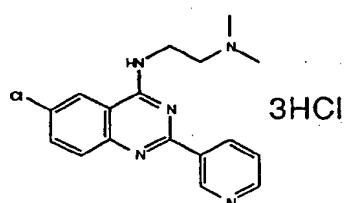
IR (KBr) v: 3425, 2500-3050, 1633, 1610, 1569, 1387, 1107 cm<sup>-1</sup>.

By the same procedure as described in Example 12, by using corresponding amine, the compounds having the following physical data was given.

#### Example 12(a)

##### 6-chloro-4-(2-dimethylaminoethyl)amino-2-(3-pyridyl)quinazoline trihydrochloride

15



20

mp = 179 °C (dec.).

NMR (200 MHz, D<sub>2</sub>O): δ 2.96 (s, 6H), 3.51 (t, 2H), 4.02 (t, 2H), 7.57 (m, 1H), 7.70 (m, 3H), 8.68 (m, 2H), 9.14 (s, 1H).

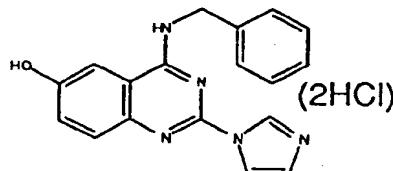
IR (KBr) v: 3405, 3215, 2545, 1577, 1536, 1474, 1437, 1396, 1360, 827, 721 cm<sup>-1</sup>.

30

#### Example 13

##### 6-hydroxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline and its salt

35



40

To 66 mg (0.2 mmol) of the compound prepared in Example 6(g) in 1 mL of acetic acid was added 0.8 mL (7 mmol) of 48% HBr in water. The mixture was heated below reflux for 23 hours then heated to full reflux for four hours. After cooling to room temperature, 15 mL of water was added to the solution and the precipitate was filtered and dried under vacuum. The material was purified on a preparative silica gel plate with 10% methanol in chloroform. Obtained 13 mg (41 μmol) of the desired product as a solid.

(free base)

50 mp : 230 °C, (dec.)

NMR (200MHz, CD3OD) δ: 4.86 (s, 2H), 7.05 (s, 1H), 7.15-7.38 (m, 4H), 7.40-7.50 (m, 3H), 7.58-7.66 (m, 1H), 7.92 (s, 1H), 8.52 (s, 1H).

IR (KBr) v: 3370, 3030, 2365, 1749, 1710, 1653, 1596, 1559, 1523, 1488, 1465, 1407, 1376, 1291, 1244, 1162, 1098, 1060, 911, 831 cm<sup>-1</sup>.

55 By the same procedure as described in Example 12, the hydrochloride having the following physical data

was given.

(2HCl salt)

mp : 155 °C, (dec.)

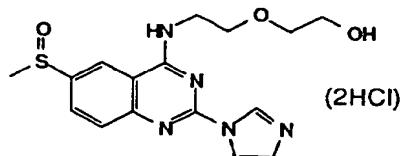
NMR (200MHz, DMSO-d<sub>6</sub>) δ: 4.92 (m, 2H), 7.22-7.77 (m, 8H), 7.86 (s, 1H), 8.38 (s, 1H), 9.36 (m, 1H), 9.94 (s, 1H).  
 IR (KBr) ν: 3395-2640, 2365, 1734, 1628, 1607, 1567, 1542, 1473, 1361, 1353, 1289, 1260, 1201, 1107, 1015, 835, 753, 702 cm<sup>-1</sup>.

5

Example 14

4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylsulfinyl-2-(1-imidazolyl)-quinazoline and its dihydrochloride

10



15

To 1.38 g of the compound prepared in example 6(mm) dissolved in 10 mL of acetic acid was added 4 mL of 30% hydrogen peroxide. The reaction was monitored by TLC. After stirring for 1/2 hour, the mixture was poured into 15 g of 50% w/w sodium hydroxide and ice. The resulting mixture was extracted four times with chloroform, dried over anhydrous magnesium sulfate and concentrated. The concentrate was triturated in ether and collected to obtain 1.26 g of the desired product as a white solid.

To 400 mg of the compound prepared above in 10 mL of methanol was added 1 mL of 10% HCl in methanol. After ten minutes, the mixture was concentrated, triturated in ether and the solid collected. Obtained 441 mg of the desired product as a dihydrochloride salt.

(free base)

mp : 144-147°C

NMR (200MHz, DMSO-d<sub>6</sub>): d 2.85(s, 3H), 3.50(m, 4H), 3.70-3.90(m, 4H), 4.59(m, 1H), 7.11(s, 1H), 7.82(m, 1H), 7.98(s, 1H), 8.02(m, 1H), 8.62(s, 1H), 8.67(m, 1H), 9.14(t, 1H).

(2HCl salt)

mp : 190-192°C

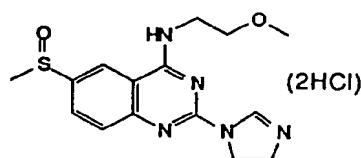
NMR (200MHz, DMSO-d<sub>6</sub>): d 2.89(s, 3H), 3.51(s, 4H), 3.76(m, 2H), 3.89(m, 2H), 7.90(m, 2H), 8.14(m, 1H), 8.45(m, 1H), 8.89(m, 1H), 9.62(t, 1H), 10.10(m, 1H).

By the same procedure as described in Example 14, by using corresponding thioether, the compounds having the following physical data were given.

Example 14(a)

4-(2-methoxyethyl)amino-6-methylsulfinyl-2-(1-imidazolyl)quinazoline and its dihydrochloride

40



45

(free base)

mp : 170-173°C

NMR (200MHz, DMSO-d<sub>6</sub>): d 2.85(s, 3H), 3.32(s, 3H), 3.69(m, 2H), 3.83(m, 2H), 7.12(s, 1H), 7.77-8.10(m, 2H), 7.98(s, 1H), 8.68(s, 1H), 9.16(s, 1H).

(2HCl salt)

mp : 191-193°C

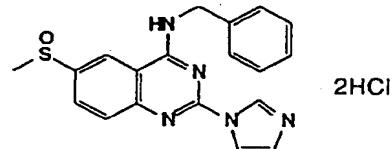
NMR (200MHz, DMSO-d<sub>6</sub>): d 2.89(s, 3H), 3.31(s, 3H), 3.67(m, 2H), 3.89(m, 2H), 7.86-8.18(m, 3H), 8.45(m, 1H), 8.89(m, 1H), 9.63(t, 1H), 10.05(m, 1H).

Example 14(b)

6-methylsulfinyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride

5

10



mp : 167-170°C.

NMR (200MHz, DMSO-d6): δ 2.87(s, 3H), 4.96(d, 2H), 7.32-7.53(m, 5H), 7.87(d, 1H), 7.93(s, 1H), 8.15(s, 1H), 8.42(s, 1H), 8.86(s, 1H), 10.01(s, 1H), 10.10(t, 1H).

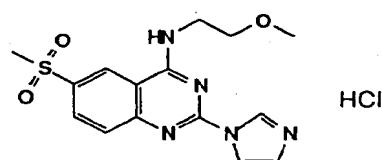
15

IR (KBr): ν 3370(w), 3220(w), 3060(m), 2825(m), 1617(s), 1577(s), 1541(m), 1497(w), 1444(m), 1396(s), 1355(w), 1014(m), 836(w), 788(w), 702(w) cm<sup>-1</sup>.

20

Example 15  
4-(2-methoxyethyl)amino-6-methylsulfonyl-2-(1-imidazolyl)quinazoline hydrochloride

25



30

To 0.63 g of the compound prepared in example 6(11) (free base) in 7 mL of acetic acid was added 3 mL of 30% hydrogen peroxide solution and the mixture was stirred at room temperature for 17 hour. The mixture was then poured into a solution of 50% w/w sodium hydroxide in ice. The resulting mixture was extracted twice with 70 mL portions of chloroform, dried over anhydrous magnesium sulfate and concentrated. The concentrate was triturated in ether and the solid collected to obtain 0.36 g of the desired product as a white powder.

35

To a suspension of 300 mg of the compound above in 15 mL of methanol was added 1 mL of 10% HCl in methanol. The mixture became clear then a precipitate formed. The mixture was concentrated to approximately 5mL, diluted with ether and filtered to obtain 319 mg of the desired product as a white solid.

40

(free base)

45

mp : 241-243 °C

(HCl salt)

mp : 226-228°C

NMR (200MHz, DMSO-d6): δ 3.32(s, 3H), 3.36(s, 3H), 3.67(m, 2H), 3.93(m, 2H), 7.81(s, 1H), 7.93(m, 1H), 8.30(m, 1H), 8.42(s, 1H), 9.16(m, 1H), 9.72(t, 1H), 9.92(s, 1H).

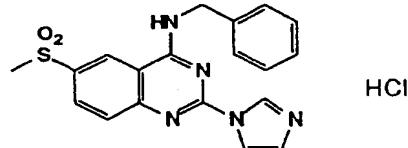
50

By the same procedure as described in Example 15, the below compound having the following physical data was given.

Example 15(a)

55

6-methylsulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline hydrochloride



mp : 125-130°C.

NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.34(s, 3H), 4.97(d, 2H), 7.31-7.50(m, 5H), 7.85(s, 1H), 7.93(d, 1H), 8.32(d, 1H), 8.44(s, 1H), 9.14(s, 1H), 9.98(s, 1H), 10.12(t, 1H).

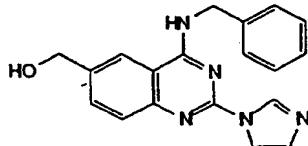
IR (KBr): ν 3230(s), 3040(s), 2705(s), 2370(m), 1616(s), 1572(s), 1524(s), 1497(m), 1399(s), 1326(s), 1258(m), 1204(w), 1147(s), 1008(m), 834(w), 783(s), 730(w), 620(w), 535(m) cm<sup>-1</sup>.

Example 16

6-hydroxymethyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline

10

15



To a suspension of 0.68 g of the compound prepared in example 5(e) in 50 mL of anhydrous tetrahydrofuran was added 2 mL of 2M lithium borohydride in tetrahydrofuran. The reaction mixture was heated at reflux for two days. The mixture was then concentrated, diluted with water and the basic solution was acidified with 1N hydrochloric acid. The resulting solution was then basified with potassium carbonate, filtered and the solid washed with water and allowed to dry. The solid material was purified on silica gel column eluting with 5% methanol in chloroform. Obtained 85 mg of the desired product.

25 mp : 173 °C (dec.).

NMR (200MHz, DMSO-d<sub>6</sub>): δ 4.67(d, 1H), 4.90(d, 1H), 5.47(t, 1H), 7.23(m, 1H), 7.25-7.51(m, 5H), 7.67-7.85(m, 2H), 8.12(m, 1H), 8.34(m, 1H), 8.91(s, 1H), 9.51(t, 1H).

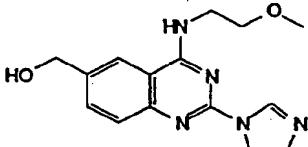
IR (KBr): ν 3445(mw), 2365(mw), 1599(s), 1559(m), 1505(mw), 1444(w), 1410(m), 1340(w), 1161(w), 1073(w) cm<sup>-1</sup>.

30 By the same procedure as described in Example 16, the below compounds having the following physical data were given.

Example 16(a)

35 4-(2-methoxyethyl)amino-6-hydroxymethyl-2-(1-imidazolyl)quinazoline

40



45 mp : 165-168°C.

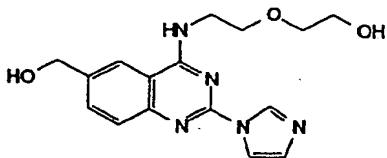
NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.35(s, 3H), 3.68(t, 2H), 3.80(t, 2H), 4.65(d, 2H), 5.45(t, 1H), 7.12(s, 1H), 7.68(m, 2H), 7.99(s, 1H), 8.27(s, 1H), 8.62(s, 1H), 8.83(s, 1H).

IR (KBr) : ν 3370(m), 1597(s), 1559(m), 1474(m), 1409(m) cm<sup>-1</sup>.

50 Example 16(b)

4-[2-(2-hydroxyethoxy)ethyl]amino-6-hydroxymethyl-2-(1-imidazolyl)-quinazoline

55

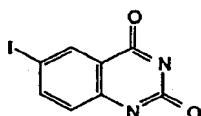


mp : 183°C.

10 NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.48(s, 4H), 3.76(m, 4H), 4.62(d, 2H), 5.44(t, 1H), 7.10(s, 1H), 7.62-7.80(m, 2H), 7.97(s, 1H), 8.27(s, 1H), 8.60(s, 1H), 8.82(bs, 1H).  
IR (KBr) : ν 3311(mw), 3156(w), 1597(s), 1558(w), 1487(w), 1438(w), 1408(ms), 1052(w) cm<sup>-1</sup>.

Reference example 18

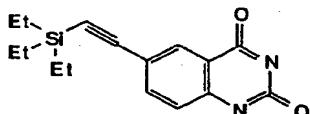
15 6-iodoquinazolin-2,4-dione



25 To a mixture of 25.36 g of 2-amino-5-iodobenzoic acid in 250 ml of water and 90 mL of THF was added 7.40 g of glacial acetic acid and stirred at room temperature. Then was added 7.82 g of potassium cyanate in water dropwise. Left to overnight. Added another 5.47 g of potassium cyanate. Stirred overnight. A total of 160 g of NaOH pellets were added portionwise, keeping the mixture cool in ice-water bath. The mixture was stirred at room temperature overnight. The mixture was cooled in a refrigerator and the precipitate filtered through a sintered glass funnel. The precipitate was then dissolved in water and acidified with 4N HCl. The precipitate was collected by filtration. The solid was dried in a vacuum oven to yield 25.44 g of the title compound.

Reference example 19

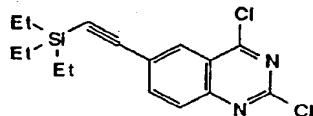
35 6-(2-triethylsilylethyl)quinazolin-2,4-dione



In a flask was placed 0.544 g of triphenylphosphine, 0.184 g of palladium chloride, and 5 mL of diethylamine. Stirred under a nitrogen atmosphere. To the resulting yellow mixture was added 75 mL of diethylamine, followed by 10.02 g of the compound prepared in reference example 18. Then added 19.8 mg of cuprous iodine to the purple suspension. Turned gray after 10 minutes. After 0.5 hr added 5.36 g of triethylsilyl acetylene and stirred at room temperature. After 3 hrs the solution turned purple. After another 1.5 hrs. the solution turned brown. Left to stir overnight. Monitored reaction by TLC. Removed the solvent under reduced pressure at 40 °C and added water. Acidified with 1N- HCl. The precipitated solid was collected by filtration, washed with water, and dried in a vacuum oven. The solid was then passed through a silica gel column, eluting with THF. After drying yielded 10.22 g of the title compound having the following physical data.  
NMR (200 MHz, DMSO-d<sub>6</sub>): δ 0.65(dd, 6H), 0.93(dd, 9H), 7.15(d, 1H), 7.69(d, 1H), 11.38(br, 2H).

Reference example 20

55 2,4-dichloro-6-(2-triethylsilylethyl)quinazoline



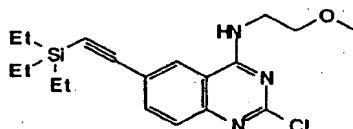
5

To 5.09 g of the compound prepared in reference example 19, was added 25 mL of  $\text{POCl}_3$  and warmed. Then added 1.03 g of N,N-dimethylaniline and heated to reflux. After 3.5 hrs, the excess  $\text{POCl}_3$  was removed under reduced pressure and the residue diluted in chloroform and poured slowly over ice. The organic layer was collected and the solvent removed. The residue was passed through a silica gel column using 20% EtOAc/hexane as a solvent. Yielded 1.4 g of the product having the following physical data.

### Reference example 21

15

#### 2-chloro-4-(2-methoxyethyl)amino-6-(2-triethylsilylethynyl)quinazoline

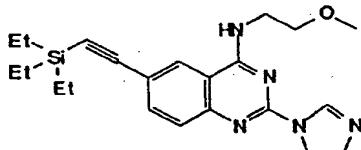


To 1.4 g of the compound prepared in reference example 20 in 20 mL of chloroform was added 2-methoxyethylamine and stirred at room temperature for 1.5 hr. Then added 4.2 ml of 1N-NaOH and heated to reflux. Left to reflux overnight. The solvent was removed under reduced pressure and the residue taken up in chloroform and water. The organic layer was collected and dried over anhydrous potassium carbonate. Removal of solvent under reduced pressure yielded 1.44 g of the title compound.

<sup>30</sup> NMR (200 MHz, CDCl<sub>3</sub>): δ 0.73 (m, 6H), 1.07(m, 9H), 3.45(s, 3H), 3.69(t, 2H), 3.88(dd, 2H), 6.32(br, 1H), 7.69(d, 1H), 7.78(dd, 1 H), 7.80(s, 1 H).

### Example 17

35 2-(1-imidazolyl)-4-(2-methoxyethyl)amino-6-(2-triethylsilylethynyl)quinazoline



To 1.32 g of the compound prepared in reference example 21 in 5 mL of ethanol was added excess imidazole (0.93 g) and heated in an oil bath to 115 °C. After 1.5 hrs. removed from heat and diluted in chloroform and washed with 1N-NaOH, collected the organic layer and washed with water. The organic layer was extracted and dried over anhydrous potassium carbonate. Removal of solvent yielded 1.33 g of the title compound. mp : 158-160 °C.

<sup>50</sup> NMR (200 MHz, DMSO- $d_6$ ): δ 0.70(q, 6H), 1.05(t, 9H), 3.30(s, 3H), 3.64(t, 2H), 3.81(dd, 2H), 7.10(s, 1H), 7.65(d, 1H), 7.78(dd, 1H), 7.96(s, 1H), 8.01(s, 1H), 8.60(s, 1H), 8.95(br, 1H).

By the same procedures as described in reference examples 18, 19, 20 and 21, and example 17, the following compound was obtained.

**55 Example 17(a)**

2-(1-imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-(2-triisopropylsilyl-ethylvinyl)guinazoline

5



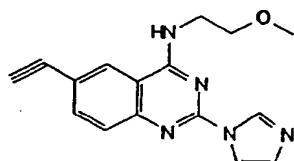
mp: 155-156 °C;

10 NMR (200MHz, CDCl<sub>3</sub>): δ 1.09 (s, 3H), 1.16 (s, 18H), 2.28 (br, 1H), 3.70 (m, 2H), 3.84 (dd, 4H), 3.95 (t, 2H), 6.65 (br, 1H), 7.14 (s, 1H), 7.68 (d, 1H), 7.75 (dd, 1H), 7.87 (s, 1H), 7.93 (s, 1H), 8.65 (s, 1H).

Example 18

15 6-ethynyl-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline

20



25 To 1.35 g of the compound prepared in example 17 in 20 mL of THF was added 3.3 mL of tetrabutylammonium fluoride (1M in THF). Stirred at room temperature for 1.5 hrs. The excess THF was removed under reduced pressure and the residue taken up in chloroform and water. The insoluble precipitate was collected by filtration. Yielded 0.83 g of the title compound.

30 NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.33(s, 1H), 3.66(m, 2H), 3.83(m, 2H), 4.34(s, 1H), 7.11(s, 1H), 7.65(d, 1H), 7.82(dd, 1H), 7.96(s, 1H), 8.57(d, 1H), 8.62(s, 1H), 8.90(broad, 1H).

IR (KBr): v 3290(s), 2945(m), 1606(s), 1559(s), 1451(s), 1352(s), 1106(s), 835(s) cm<sup>-1</sup>.

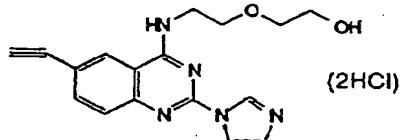
By the same procedure as described in example 18, the following compound was given.

35

Example 18(a)

2-(1-imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-ethynylquinazoline and its salt

40



45

(free base)

mp : 166-167°C;

NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.50 (s, 4H), 3.78 (m, 4H), 4.35 (s, 1H), 4.59 (t, 1H), 7.10 (s, 1H), 7.65 (d, 1H), 7.80 (dd, 1H), 7.97 (s, 1H), 8.55 (d, 1H), 8.61 (s, 1H), 8.90 (br, 1H).

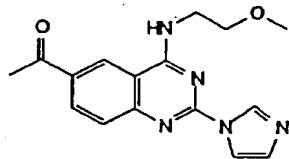
50 (HCl salt)

mp : 178 °C;

NMR (200MHz, DMSO-d<sub>6</sub>): δ 3.51 (s, 4H), 3.87 (m, 2H), 4.44 (s, 1H), 7.73 (d, 1H), 7.82 (s, 1H), 7.90 (d, 1H), 8.40 (s, 1H), 8.67 (s, 1H), 9.25 (br, 1H).55 Example 19

6-acetyl-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline

5



To 0.541 g of the compound prepared in example 18 in 10 ml of acetic acid was added 0.7 mL of 10% H<sub>2</sub>SO<sub>4</sub> and 0.10 g of mercury II sulfate and heated to reflux. After 2 hours removed from heat and basified. The yellow precipitate was filtered. The solid was washed with THF. Removed the solvent under reduced pressure and titrated the residue in 50 % ether/pentane. The solid was collected by filtration. Yielded 0.063 g of the desired product.

mp : 208-210 °C.  
NMR (200MHz, CDCl<sub>3</sub>): δ 2.64(s, 1H), 3.49(s, 3H), 3.79(t, 2H), 3.95(q, 2H), 7.00(broad, 1H), 7.16(t, 1H), 7.74(d, 1H), 7.95(t, 1H), 8.17(dd, 1H), 8.42(d, 1H), 8.67(t, 1H).

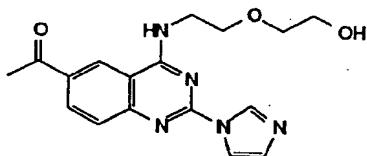
By the same procedure as described in Example 19, the below compound having the following physical data was given.

20 Example 19(a)

4-[2-(2-hydroxyethoxy)ethyl]amino-6-acetyl-2-(1-imidazolyl)quinazoline

25

30



mp : 164-166°C.

NMR (200MHz, DMSO-d<sub>6</sub>): δ 2.69(s, 3H), 3.51 (s, 4H), 3.76(m, 2H), 3.84(t, 2H), 4.60(br, 1H), 7.12(s, 1H), 7.73(d, 1H), 7.98(s, 1H), 8.27(dd, 1H), 8.64(s, 1H), 9.00(s, 1H), 9.25(br, 1H).

IR (KBr) : n 3350, 1671, 1623, 1593, 1558, 1474, 1447, 1418, 1365, 1307, 1270, 1111, 1051 cm<sup>-1</sup>.

Formulation Example 1

40 The following components were admixed in conventional method and punched out to obtain 100 tablets each containing 50 mg of active ingredient.

45

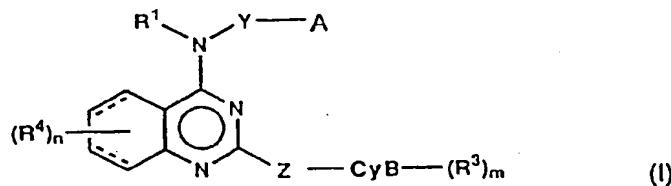
4-phenylmethylamino-2-(3-pyridyl)quinazoline	— 5.0 g
cellulose calcium glycolate (disintegrating agent)	— 0.2 g
magnesium stearate (lubricating agent)	— 0.1 g
micro crystalline cellulose	— 4.7 g

50

**Claims**

1. A quinazoline derivative of the formula:

55



10 wherein — represents a single or double bond;

R<sup>1</sup> is hydrogen or C<sub>1-4</sub> alkyl;

Y is a single bond or C<sub>1-6</sub> alkylene;

A is

- (i) -CyA-(R<sup>2</sup>)<sub>l</sub>,
- (ii) -O-R<sup>0</sup> or -S(O)<sub>p</sub>-R<sup>0</sup>, or
- (iii) -NR<sup>16</sup>R<sup>17</sup>;

in which R<sup>0</sup> is hydrogen, C<sub>1-4</sub> alkyl, hydroxy-C<sub>1-4</sub> alkyl or -CyA-(R<sup>2</sup>)<sub>l</sub>;

R<sup>16</sup> and R<sup>17</sup> independently are hydrogen or C<sub>1-4</sub> alkyl;

20 p is 0-2;

CyA is

- (1) a 3-7 membered, saturated or unsaturated carbocycle,
- (2) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom,
- (3) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom and one oxygen atom,
- (4) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom and two oxygen atoms,
- (5) a 4-7 membered, unsaturated or partially saturated heterocycle containing two nitrogen atoms and one oxygen atom,
- (6) a 4-7 membered, unsaturated or partially saturated heterocycle containing one or two sulfur atoms,
- (7) a 4-7 membered, unsaturated, partially saturated or fully saturated heterocycle containing one or two oxygen atoms;

30 R<sup>2</sup> is (1) hydrogen, (2) C<sub>1-4</sub> alkyl, (3) C<sub>1-4</sub> alkoxy, (4) -COOR<sup>5</sup>, in which R<sup>5</sup> is hydrogen or C<sub>1-4</sub> alkyl, (5) -NR<sup>8</sup>R<sup>7</sup>, in which R<sup>8</sup> and R<sup>7</sup> independently are hydrogen or C<sub>1-4</sub> alkyl, (6) -SO<sub>2</sub>NR<sup>8</sup>R<sup>7</sup>, in which R<sup>8</sup> and R<sup>7</sup> are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro or (10) trifluoromethoxy;

35 Z is a single bond, methylene, ethylene, vinylene or ethynylene;

CyB is

- (1) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom,
- (2) a 4-7 membered, unsaturated or partially saturated heterocycle containing two nitrogen atoms,
- (3) a 4-7 membered, unsaturated or partially saturated heterocycle containing three nitrogen atoms,
- (4) a 4-7 membered, unsaturated or partially saturated heterocycle containing one or two oxygen atoms,
- (5) a 4-7 membered, unsaturated or partially saturated heterocycle containing one or two sulfur atoms,

40 R<sup>3</sup> is hydrogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, halogen or trifluoromethyl;

R<sup>4</sup> is (1) hydrogen, (2) C<sub>1-4</sub> alkyl, (3) C<sub>1-4</sub> alkoxy, (4) -COOR<sup>8</sup>, in which R<sup>8</sup> is hydrogen or C<sub>1-4</sub> alkyl, (5) -NR<sup>9</sup>R<sup>10</sup>, in which R<sup>9</sup> is hydrogen, C<sub>1-4</sub> alkyl or phenyl(C<sub>1-4</sub> alkyl) and R<sup>10</sup> is hydrogen or C<sub>1-4</sub> alkyl, (6)

-NHCOR<sup>11</sup>, in which R<sup>11</sup> is C<sub>1-4</sub> alkyl, (7) -NHSO<sub>2</sub>R<sup>11</sup>, in which R<sup>11</sup> is as hereinbefore defined, (8)

SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup> in which R<sup>9</sup> and R<sup>10</sup> are as hereinbefore defined, (9) -OCOR<sup>11</sup>, in which R<sup>11</sup> is as hereinbefore

defined, (10) halogen, (11) trifluoromethyl, (12) hydroxy, (13) nitro, (14) cyano, (15) -SO<sub>2</sub>N=CHNR<sup>12</sup>R<sup>13</sup>

50 in which R<sup>12</sup> is hydrogen or C<sub>1-4</sub> alkyl and R<sup>13</sup> is C<sub>1-4</sub> alkyl, (16) -CONR<sup>14</sup>R<sup>15</sup> in which R<sup>14</sup> is hydrogen or

C<sub>1-4</sub> alkyl or phenyl(C<sub>1-4</sub> alkyl) and R<sup>15</sup> is C<sub>1-4</sub> alkyl or (17) C<sub>1-4</sub> alkylthio, (18) C<sub>1-4</sub> alkylsulfinyl, (19)

C<sub>1-4</sub> alkylsulfonyl, (20) ethynyl, (21) hydroxymethyl, (22) tri(C<sub>1-4</sub> alkyl)silylethyne or (23) acetyl;

and l, m and n independently are 1 or 2;

with the proviso that

- (1) CyA-(R<sup>2</sup>)<sub>l</sub> does not represent cyclopentyl or trifluoromethylphenyl when Y is a single bond,
- (2) CyB does not bond to Z through a nitrogen atom when Z is vinylene or ethynylene,
- (3) CyB is not pyridine or thiophene when CyA is a 4-7 membered unsaturated, partially saturated or fully saturated heterocycle containing one or two oxygen atoms, and

(4) Y is not a single bond when A is (ii) -O-R<sup>0</sup> or -S(O)<sub>p</sub>-R<sup>0</sup> or (iii) -NR<sup>16</sup>R<sup>17</sup>;  
or a pharmaceutically acceptable salt thereof, or a hydrate thereof.

2. A compound according to claim 1, wherein CyB is a pyridine ring, an imidazole ring, a triazole or pyrrole ring, or a furan or thiophene ring.

3. A compound according to claim 1 or 2, wherein CyA is a benzene ring, a cyclopropyl ring, a cyclohexyl ring, a pyridine ring, a pyrrole or isoxazole ring, a thiophene ring, or a furan, tetrahydrofuran or pyran ring.

4. A compound according to claim 1, 2 or 3 wherein A is OH, -O-C<sub>1-4</sub> alkyl, -O-C<sub>1-4</sub> alkyl-OH, -S(O)<sub>p</sub>-C<sub>1-4</sub> alkyl, or -NR<sup>16</sup>R<sup>17</sup>.

5. A compound according to any one of claims 1 to 4, wherein Y is a single bond, methylene or ethylene.

6. A compound according to any one of claims 1 to 5, wherein Z is a single bond, methylene, or vinylene.

15. 7. A compound according to any one of the preceding claims, which is:

4-phenylmethylamino-2-(3-pyridyl)quinazoline,

4-(3-methylphenylmethyl)amino-2-(3-pyridyl)quinazoline,

4-(3,4-dimethoxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,

20. 4-(4-carboxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,

4-(3-methoxycarbonylphenylmethyl)amino-2-(3-pyridyl)quinazoline,

4-(4-(N,N-dimethylamino)phenylmethyl)amino-2-(3-pyridyl)quinazoline,

4-(4-sulfamoylphenylmethyl)amino-2-(3-pyridyl)quinazoline,

4-(3-chlorophenylmethyl)amino-2-(3-pyridyl)quinazoline,

25. 4-(3-trifluoromethylphenylmethyl)amino-2-(3-pyridyl)quinazoline,

4-(3-nitrophenylmethyl)amino-2-(3-pyridyl)quinazoline,

4-phenylmethylamino-2-(6-methyl-3-pyridyl)quinazoline,

4-phenylmethylamino-2-(6-methoxy-3-pyridyl)quinazoline,

4-phenylmethylamino-2-(6-chloro-3-pyridyl)quinazoline,

30. 4-phenylmethylamino-2-(6-trifluoromethyl-3-pyridyl)quinazoline,

4-phenylmethylamino-6-methyl-2-(3-pyridyl)quinazoline,

4-phenylmethylamino-6-methoxy-2-(3-pyridyl)quinazoline,

4-phenylmethylamino-6,7-dimethoxy-2-(3-pyridyl)quinazoline,

4-phenylmethylamino-6-carboxy-2-(3-pyridyl)quinazoline,

35. 4-phenylmethylamino-6-methoxycarbonyl-2-(3-pyridyl)quinazoline,

4-phenylmethylamino-6-amino-2-(3-pyridyl)quinazoline,

4-phenylmethylamino-6-(N,N-dimethylamino)-2-(3-pyridyl)quinazoline,

4-phenylmethylamino-6-acetylamino-2-(3-pyridyl)quinazoline,

4-phenylmethylamino-6-méthanesulfonylamino-2-(3-pyridyl)quinazoline,

40. 4-phenylmethylamino-6-sulfamoyl-2-(3-pyridyl)quinazoline,

4-phenylmethylamino-6-acetoxy-2-(3-pyridyl)quinazoline,

4-phenylmethylamino-6-chloro-2-(3-pyridyl)quinazoline,

4-phenylmethylamino-6-bromo-2-(3-pyridyl)quinazoline,

4-phenylmethylamino-7-fluoro-2-(3-pyridyl)quinazoline,

45. 4-phenylmethylamino-6-trifluoromethyl-2-(3-pyridyl)quinazoline,

4-phenylmethylamino-6-trifluoromethoxy-2-(3-pyridyl)quinazoline,

4-phenylmethylamino-6-hydroxy-2-(3-pyridyl)quinazoline,

4-phenylmethylamino-6-nitro-2-(3-pyridyl)quinazoline,

4-phenylmethylamino-6-cyano-2-(3-pyridyl)quinazoline,

50. 4-phenylmethylamino-6-methyl-2-(4-pyridyl)quinazoline,

4-phenylmethylamino-6-methoxy-2-(4-pyridyl)quinazoline,

4-phenylmethylamino-6,7-dimethoxy-2-(4-pyridyl)quinazoline,

4-phenylmethylamino-6-carboxy-2-(4-pyridyl)quinazoline,

4-phenylmethylamino-6-methoxycarbonyl-2-(4-pyridyl)quinazoline,

55. 4-phenylmethylamino-6-amino-2-(4-pyridyl)quinazoline,

4-phenylmethylamino-6-(N,N-dimethylamino)-2-(4-pyridyl)quinazoline,

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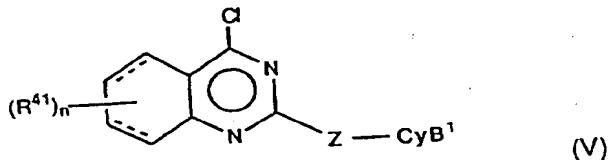
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 4-phenylmethylamino-6-cyano-2-(4-pyridyl)quinazoline,  
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 10 4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylthio-2-(1-imidazolyl)quinazoline,  
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 15 4-phenylmethylamino-6-methoxy-2-(1-imidazolyl)quinazoline,  
 4-phenylmethylamino-6,7-dimethoxy-2-(1-imidazolyl)quinazoline,  
 4-phenylmethylamino-6-carboxy-2-(1-imidazolyl)quinazoline,  
 4-phenylmethylamino-6-methoxycarbonyl-2-(1-imidazolyl)quinazoline,  
 4-phenylmethylamino-6-amino-2-(1-imidazolyl)quinazoline,  
 4-phenylmethylamino-6-(N,N-dimethylamino)-2-(1-imidazolyl)quinazoline,  
 20 4-phenylmethylamino-6-acetylamino-2-(1-imidazolyl)quinazoline,  
 4-phenylmethylamino-6-methanesulfonylamino-2-(1-imidazolyl)quinazoline,  
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 25 4-phenylmethylamino-6-bromo-2-(1-imidazolyl)quinazoline,  
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 7-chloro-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
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 6-nitro-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 40 6-methoxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
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 6-dimethylaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 6,7-dimethoxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 45 4-(3,4-dimethoxyphenyl)methyl)amino-2-(1-imidazolyl)quinazoline,  
 6-dimethylaminomethyleneaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 6-(phenylmethylaminosulfonyl)-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 4-(2-phenylethyl)amino-2-(1-imidazolyl)quinazoline,  
 4-cyclohexylmethylamino-2-(1-imidazolyl)quinazoline,  
 50 6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 6-phenylmethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 6-iodo-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 6-ethoxycarbonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 6-hydroxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 4-(4-trifluoromethoxyphenyl)methyl)amino-2-(1-imidazolyl)quinazoline,  
 55 4-phenylmethylamino-2-(2-azepinyl)quinazoline,  
 4-phenylmethylamino-2-(1,5-diazepin-2-yl)quinazoline,  
 4-phenylmethylamino-2-(2-pyrimidinyl)quinazoline,  
 4-phenylmethylamino-2-(2-triazinyl)quinazoline,

4-phenylmethylamino-2-(2-pyrrolyl)quinazoline,  
 4-phenylmethylamino-2-(1-triazolyl)quinazoline,  
 6-hydroxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,  
 4-(3-trifluoromethoxyphenyl)methylamino-2-(1-imidazolyl)quinazoline  
 5 4-phenylmethylamino-6,8-diiodo-2-(1-imidazolyl)quinazoline,  
 4-(2-phenoxyethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,  
 6-hydroxymethyl-4-phenylmethylamino-2-(3-pyridyl)quinazoline  
 10 6-methylthio-4-phenylmethylamino-2-(3-pyridyl)quinazoline,  
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 6-methylsulfinyl-4-phenylmethylamino-2-(3-pyridyl)quinazoline,  
 4-phenylmethylamino-2-(2-thienyl)quinazoline,  
 4-phenylmethylamino-2-(2-furyl)quinazoline,  
 4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,  
 15 6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,  
 6-ethoxycarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,  
 6-ethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,  
 4-(2-methoxyethyl)amino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline or  
 20 4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline.

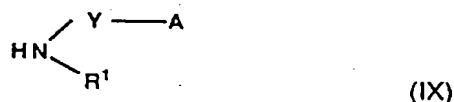
20 8. A process for the preparation of a 4-aminoquinazoline derivative of formula (I) as defined in claim 1, comprising:

(a) reacting a compound of the formula:

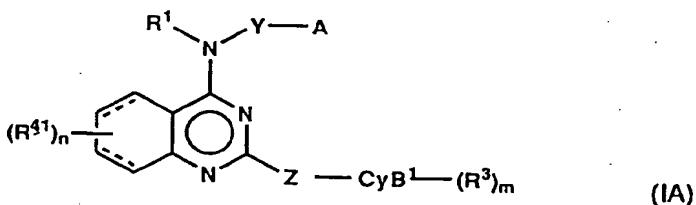


wherein R<sup>41</sup> is (1) hydrogen, (2) C<sub>1-4</sub> alkyl, (3) C<sub>1-4</sub> alkoxy, (4) -COOR<sup>8</sup> wherein R<sup>8</sup> is hydrogen or C<sub>1-4</sub> alkyl, (5) -NR<sup>9</sup>R<sup>10</sup> in which R<sup>9</sup> and R<sup>10</sup> are as hereinbefore defined, provided that R<sup>9</sup> and R<sup>10</sup> are not both hydrogen, (6) SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, in which R<sup>9</sup> and R<sup>10</sup> are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro, (10) cyano, (11) C<sub>1-4</sub> alkylthio, (12) tri(C<sub>1-4</sub> alkyl)silyl ethynyl, (13) -SO<sub>2</sub>N=CHNR<sup>12</sup>R<sup>13</sup>, in which R<sup>12</sup> is hydrogen or C<sub>1-4</sub> alkyl and R<sup>13</sup> is C<sub>1-4</sub> alkyl or (14) -CONR<sup>14</sup>R<sup>15</sup> in which R<sup>14</sup> is hydrogen or C<sub>1-4</sub> alkyl or phenyl(C<sub>1-4</sub> alkyl) and R<sup>15</sup> is C<sub>1-4</sub> alkyl, CyB<sup>1</sup> is as defined in claim 1 for CyB, provided that CyB<sup>1</sup> bonds to Z through a carbon atom in the CyB<sup>1</sup> ring, and the other symbols are as defined in claim 1, with a compound of the formula:

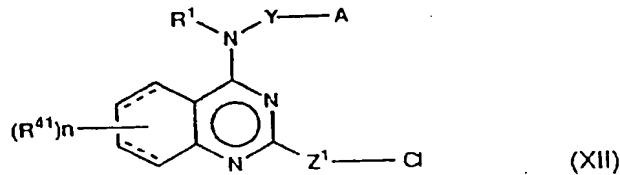
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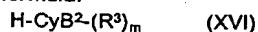
wherein all the symbols are as defined in claim 1, to give a compound of the formula (IA):



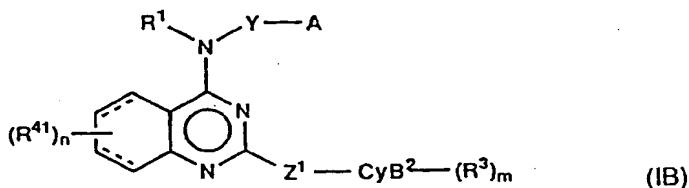
wherein R<sup>41</sup> and CyB<sup>1</sup> are as defined above and the other symbols are as defined in claim 1;  
 (b) reacting a compound of the formula:



wherein R<sup>41</sup> is as defined above, Z<sup>1</sup> is a single bond or methylene, and the other symbols are as defined in claim 1, with a compound of the formula:

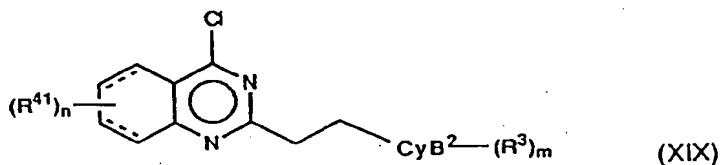


wherein CyB<sup>2</sup> is as defined in claim 1 for CyB, provided that CyB<sup>2</sup> bonds to Z<sup>1</sup> through a nitrogen atom in the CyB<sup>2</sup> ring, and the other symbols are as defined in claim 1, to give a compound of the formula (IB):



wherein R<sup>41</sup>, Z and CyB<sup>2</sup> are as defined above and the other symbols are as defined in claim 1; or

(c) reacting a compound of the formula:

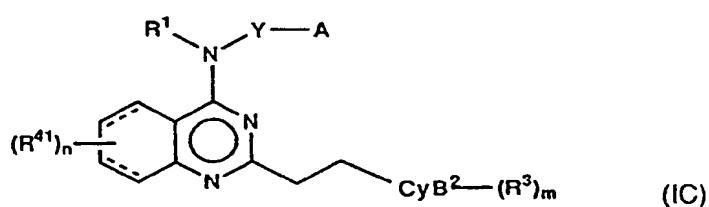


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wherein R<sup>41</sup> and CyB<sup>2</sup> are as defined above and the other symbols are as defined in claim 1 with a compound of the formula:



wherein all the symbols are as defined in claim 1, to give a compound of the formula (IC):



wherein R<sup>41</sup> and CyB<sup>2</sup> are as defined above and the other symbols are as defined in claim 1; and optionally converting the compound of formula (I) thus obtained into another compound of formula (I).

5        9. A pharmaceutical composition for the treatment of mammals, including humans, comprising as active ingredient, an effective amount of a compound of the formula (I), a pharmaceutically acceptable salt thereof or a hydrate thereof in association with a pharmaceutically acceptable carrier or coating.

10      10. A compound of the formula (I) as defined in claim 1, a pharmaceutically acceptable salt thereof or a hydrate thereof, for use as a medicament in the treatment of mammals.

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European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number  
EP 93 30 5557

DOCUMENTS CONSIDERED TO BE RELEVANT									
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.)						
A	EP-A-0 135 975 (AKZO) * page 1 - page 13 *	1,2,8-10	C07D401/04 C07D401/06 C07D405/04 C07D409/04 C07D413/14 C07D401/14 C07D409/14 A61K31/505						
A	GB-A-2 002 746 (GIST-BROCADES) * the whole document *	1,2,8-10							
D, A	CH-A-578 556 (SANDOZ) * page 1 - page 4 *	1,8-10							
A	FR-A-2 310 756 (SANDOZ) * the whole document *	1,2,8-10							
A	FR-A-2 102 221 (SQUIBB & SONS) * page 1 - page 11 *	1,2,8-10							
A	FR-A-2 081 456 (THE NORWICH PHARMACAL COMPANY) * page 1 - page 8 *	1,2,8-10							
A	FR-A-1 460 221 (THE NORWICH PHARMACAL COMPANY) * page 1 - page 5 *	1,2,8-10							
			TECHNICAL FIELDS SEARCHED (Int.Cl.) C07D						
<p>The present search report has been drawn up for all claims</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">Place of search</td> <td style="width: 33%;">Date of compilation of the search</td> <td style="width: 34%;">Examiner</td> </tr> <tr> <td>THE HAGUE</td> <td>27 October 1993</td> <td>FRANCOIS, J.</td> </tr> </table> <p><b>CATEGORY OF CITED DOCUMENTS</b></p> <p>X : particularly relevant if taken alone      Y : particularly relevant if combined with another document of the same category      A : technological background      O : non-written disclosure      P : intermediate document</p> <p>T : theory or principle underlying the invention      E : earlier patent document, but published on, or after the filing date      D : document cited in the application      L : document cited for other reasons      A : member of the same patent family, corresponding document</p>				Place of search	Date of compilation of the search	Examiner	THE HAGUE	27 October 1993	FRANCOIS, J.
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THE HAGUE	27 October 1993	FRANCOIS, J.							